STIC Search Report

Biotech-Chem Library

STIC Database Tracking Number: 157930

TO: Rebecca Cook **Location: REM/3A71/3C70** **Art Unit: 1614** **_____, 2005** **Case Serial Number: 10/625152**	**From: P. Sheppard** **Location: Remsen Building** **Phone: (571) 272-2529** **sheppard@uspto.gov**

Search Notes

Access DB# 159930

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Rellina Look Examiner #: 69826 Date: 6/29/05
Art Unit: 1614 Phone Number 30 Serial Number: 10/625,152
Mail Box and Bldg/Room Location: 3C70 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

Earliest Priority Filing Date: _____

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search 1) compound of claim 1 when R_5 is O
" " " R_5 is C=O
2)
3) prodrugs of 1)
4) " " 2)
5) drugs that lower serum estradiol & their use to treat prostate cancer.
6) metabolism of prodrugs - see limitation of Claim 20. metabolism converting esters to OH; H to OH eg
7) a) generic concepts of prodrugs Thank you
b) moieties known to be used to make prodrugs Rellina
c) difficulties in determining which moieties yield useful prodrugs.
8) differences in treatment of cancer dependent

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STAFF USE ONLY Type of Search Vendor and cost where applicable
Searcher: _____ NA Sequence (#)_____ STN _____

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FILE COVERS 1907 - 26 Jul 2005  VOL 143 ISS 5
FILE LAST UPDATED: 25 Jul 2005  (20050725/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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L1                STR
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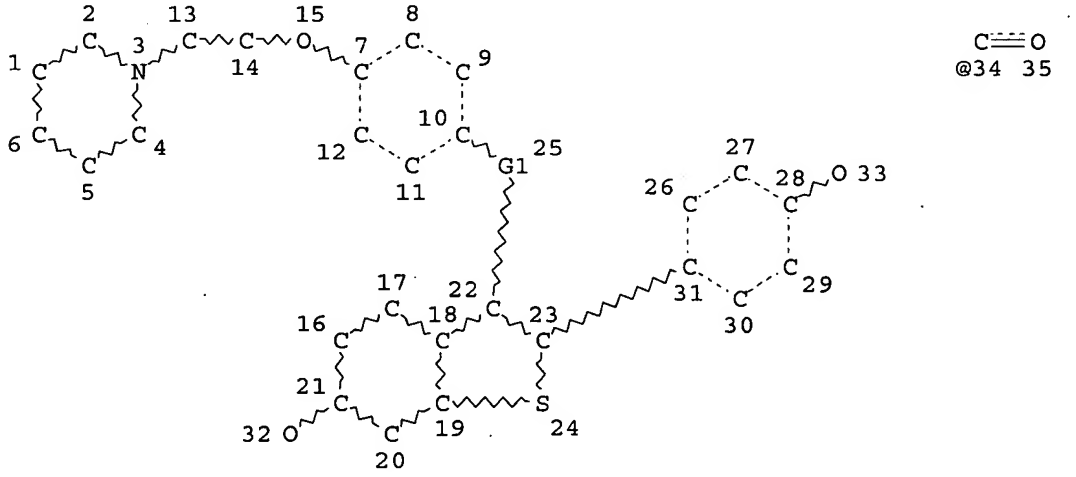


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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
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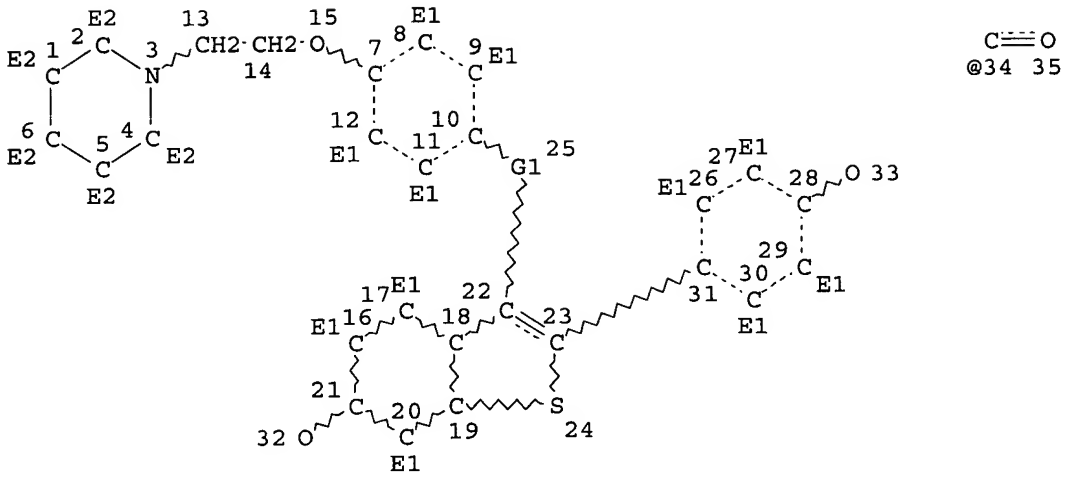

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L9 42118 SEA FILE=HCAPLUS ABB=ON PLU=ON ("PROSTATE CANCER"/CV OR "PROSTATE GLAND, NEOPLASM"/CV) OR PROSTATE?
L10 16 SEA FILE=HCAPLUS ABB=ON PLU=ON L8(L)L9

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L10 ANSWER 1 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:480268 HCAPLUS
DOCUMENT NUMBER: 143:71239

TITLE: Inhibition of prostate carcinogenesis in probasin/SV40 T antigen transgenic rats by raloxifene, an antiestrogen with anti-androgen action, but not nimesulide, a selective cyclooxygenase-2 inhibitor

AUTHOR(S): Zeng, Yu; Yokohira, Masanao; Saoo, Kousuke; Takeuchi, Hijiri; Chen, Yan; Yamakawa, Keiko; Matsuda, Yoko; Kakehi, Yoshiyuki; Imaida, Katsumi

CORPORATE SOURCE: Onco-Pathology, Department of Pathology and Host-Defense, Department of Urology, Faculty of Medicine, Kagawa University, Kagawa, 761-0793, Japan

SOURCE: Carcinogenesis (2005), 26(6), 1109-1116
CODEN: CRNGDP; ISSN: 0143-3334

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

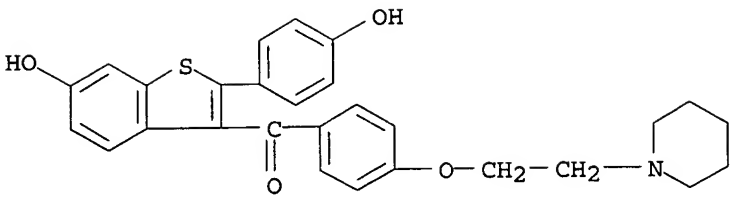
LANGUAGE: English

AB The chemopreventive efficacies of raloxifene and nimesulide, an anti-estrogen but with anti-androgen action and a cyclooxygenase-2 (COX-2) selective inhibitor, resp., were evaluated in probasin/SV40 T antigen (Tag) transgenic (TG) rats. The treatment groups were placebo, nimesulide (400 ppm in basal diet p.o.), raloxifene (slow-release pellets implanted s.c., 5 mg/kg/day), raloxifene (5 mg/kg/day) plus nimesulide (400 ppm), and raloxifene (10 mg/kg/day) plus nimesulide (400 ppm). Animals were killed at 17 wk of age, and prostate tissues were harvested and weighed by lobes. Tissues were evaluated by histol., immunohistochem., and western blot analyses and blood was collected to measure the testosterone levels. All the animals in the placebo group had tumors in each lobe compared with only 43% each in the dorsolateral (DLP) and anterior prostate (AP) of the animals treated with raloxifene (10 mg/kg/day) plus nimesulide. The total prostate wts. and adenocarcinoma portions were significantly reduced in the three raloxifene-treated groups, whereas atrophic glands were increased. There were no significant differences between the nimesulide alone and placebo groups or between the raloxifene (5 mg/kg/day) alone and raloxifene (5 mg/kg/day) plus nimesulide group, suggesting a lack of cancer preventive effects of the COX-2 inhibitor in this animal model. PCNA pos. rates in ventral prostate (VP) and DLP, and androgen receptor (AR) levels in VP were significantly reduced in the three raloxifene-treated groups. Furthermore, circulating testosterone was decreased after raloxifene (10 mg/kg/day) plus nimesulide treatment. These results demonstrate that raloxifene, but not nimesulide, inhibits prostate carcinogenesis in SV40 Tag TG rats associated with a decline in circulating testosterone levels and a loss of AR expression, as well as an inhibition of cell proliferation.

IT **84449-90-1**, Raloxifene
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of **prostate** carcinogenesis in probasin/SV40 T antigen transgenic rats by raloxifene, an antiestrogen with anti-androgen action, but not nimesulide, a selective cyclooxygenase-2 inhibitor)

RN 84449-90-1 HCAPLUS

CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:364888 HCAPLUS
TITLE: Steroid hormone receptors as targets for the therapy of breast and prostate cancer-recent advances, mechanisms of resistance, and new approaches
AUTHOR(S): Hoffmann, J.; Sommer, A.
CORPORATE SOURCE: Research Laboratories of Schering AG, Berlin, 13342, Germany
SOURCE: Journal of Steroid Biochemistry and Molecular Biology (2005), 93(2-5), 191-200
CODEN: JSBBEZ; ISSN: 0960-0760
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

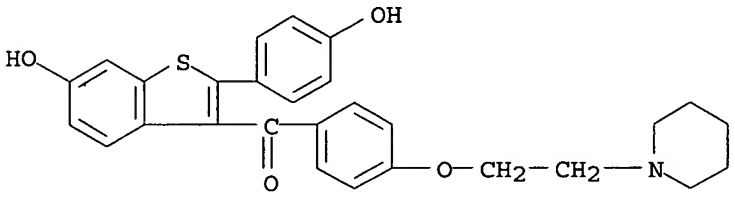
AB Surgical ovariectomy and orchiectomy, first proposed over a century ago, are effective in breast and prostate cancer therapy, resp. Later, the discovery of steroid hormones and their nuclear receptors led to the concept that inhibition of steroid receptor function by an antagonist prevents tumor growth. While the first anti-hormones, cyproteroneacetate (CPA) and tamoxifen were found accidentally, deeper understanding of nuclear receptors as transcription factors enabled more rational, structure-activity based drug discovery. Results from a drug-finding program on pure anti-estrogens will be reported. These new steroidal anti-estrogens are highly active, pure ER-antagonists that lead to an efficient degradation of the estrogen receptor α (ERα) protein without any agonistic activity. Data obtained in preclin. tumor models in mice and rats showed a high potency in growth inhibition of ERα-pos. breast cancer. In parallel, by comparing three independently generated anti-estrogen-resistant breast cancer cell lines, it was our intention to gain insight into the mechanisms of endocrine resistance which will allow to define new approaches for the treatment of endocrine-resistant breast cancer. Candidate proteins potentially involved in mechanisms of anti-estrogen-resistant growth of breast cancer cell lines were analyzed. ERα and progesterone receptor (PR) expressions were lost on the protein level in all three anti-estrogen-resistant cell lines, whereas binding of epidermal growth factor (EGF) and protein expression of epidermal growth factor receptor (EGFR) were increased. Loss of ERα expression may be linked to the acquisition of anti-estrogen resistance and enhanced expression of the EGFR and of members of the S100 family of Ca2+-binding proteins may contribute to the outgrowth of resistant cells. Furthermore, we describe the pharmacol. development of a novel, highly potent progesterone receptor antagonist. In rat mammary tumor models, treatment with the PR antagonist completely suppressed the growth of established tumors and prevented the development of breast tumors. Advanced prostate cancer is effectively treated by androgen ablation. However, this therapy becomes inefficient although the androgen receptor (AR) is still functionally expressed. One novel strategy for the

treatment of advanced prostate cancer could be the selective inhibition of AR protein expression by anti-sense oligonucleotides or small interfering RNA (siRNA) mols. Down-regulation of the human AR caused significant inhibition of LNCaP prostate cancer growth in vivo. Taken together, many promising alternatives for endocrine therapy of breast and prostate cancer are arising.

IT **84449-90-1**, Raloxifene
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(steroid hormone receptors as targets for breast and **prostate** cancer treatment and their role in antitumor resistance)

RN 84449-90-1 HCAPLUS

CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:965090 HCAPLUS
DOCUMENT NUMBER: 141:389284
TITLE: Methods and compositions using gonadotropin hormone releasing hormone
INVENTOR(S): Porchet, Herve; Heimgartner, Frederic; Curdy, Catherine; Ducrey, Bertrand
PATENT ASSIGNEE(S): Debiopharm S.A., Switz.
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004096259	A1	20041111	WO 2004-IB1334	20040430

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2003-IB1680 A 20030430

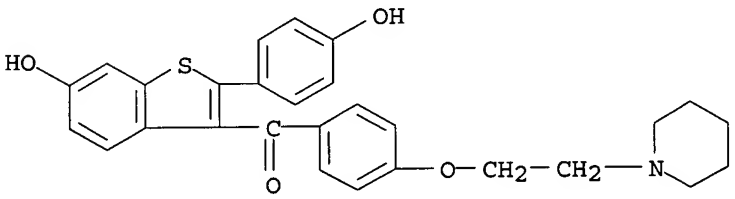
AB The present invention relates to compns. comprising two sustained release formulations, the first being capable of releasing a gonadotropin

releasing hormone composition and the second an estrogenic composition The compns.
of the invention can be employed for an improved androgen deprivation therapy of prostate cancer, in which therapy loss of bone mineral d. and the occurrence and severity of hot flashes are minimized through the maintenance of a minimally adequate estrogen level.

IT **84449-90-1**, Raloxifene
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(gonadotropin hormone-releasing hormone formulations for improved androgen deprivation in **prostate** cancer therapy)

RN 84449-90-1 HCAPLUS

CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



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L10 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:739987 HCAPLUS
DOCUMENT NUMBER: 141:218950
TITLE: Method using toremifene and related compounds for the treatment and chemoprevention of prostate cancer
INVENTOR(S): Steiner, Mitchell S.; Raghow, Sharan
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. Ser. No. 611,056.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004176470	A1	20040909	US 2003-747685	20031230
US 6265448	B1	20010724	US 1999-306958	19990507
EP 1475087	A2	20041110	EP 2004-18861	19990507
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, LT, LV, FI, RO, MK, CY, AL				
US 6413533	B1	20020702	US 2000-531472	20000320
US 6632447	B1	20031014	US 2000-707766	20001108
US 2004092602	A1	20040513	US 2003-611056	20030702

PRIORITY APPLN. INFO.:

US 1998-84602P	P	19980507
US 1999-306958	A2	19990507
US 1999-436208	B2	19991108
US 2000-531472	A2	20000320
US 2000-707766	A2	20001108
US 2003-611056	A2	20030702

	EP 1999-924157	A3 19990507
	US 2000-660184	A2 20000912
	US 2000-660191	A2 20000912
	US 2000-660197	A2 20000912
	US 2002-300939	A2 20021121

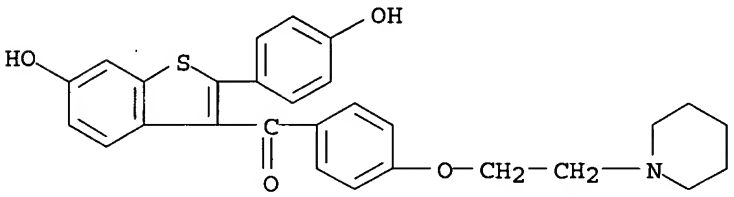
OTHER SOURCE(S): MARPAT 141:218950

AB This invention discloses methods for treating a subject with pre-malignant lesions of prostate cancer, as well as methods for suppressing, inhibiting or reducing the incidence of pre-malignant lesions of prostate cancer. The methods of the invention make use of toremifene and related compds.

IT **84449-90-1**, Raloxifene
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(toremifene and related compds. for treatment and chemoprevention of **prostate** cancer)

RN 84449-90-1 HCAPLUS

CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



L10 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	2004:676569 HCAPLUS
DOCUMENT NUMBER:	141:271320
TITLE:	Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: A randomized controlled trial
AUTHOR(S):	Smith, Matthew R.; Fallon, Mary Anne; Lee, Hang; Finkelstein, Joel S.
CORPORATE SOURCE:	Division of Hematology and Oncology, Massachusetts General Hospital, Boston, MA, 02114, USA
SOURCE:	Journal of Clinical Endocrinology and Metabolism (2004), 89(8), 3841-3846 CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER:	Endocrine Society
DOCUMENT TYPE:	Journal
LANGUAGE:	English

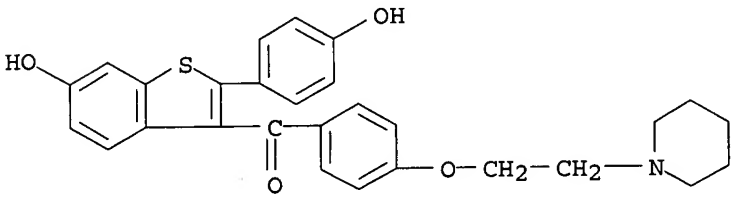
AB GnRH agonists decrease bone mineral d. and increase fracture risk in men with prostate cancer. Raloxifene increases bone mineral d. in postmenopausal women, but its efficacy in hypogonadal men is not known. In a 12-mo open-label study, men with nonmetastatic prostate cancer (n = 48) who were receiving a GnRH agonist were assigned randomly to raloxifene (60 mg/d) or no raloxifene. Bone mineral densities of the posteroanterior lumbar spine and proximal femur were measured by dual energy x-ray absorptiometry. Mean (±SE) bone mineral d. of the posteroanterior lumbar spine increased by 1.0 ± 0.9% in men treated with raloxifene and decreased by 1.0 ± 0.6% in men who did not receive raloxifene (P = 0.07). Bone mineral d. of the total hip increased by 1.1 ± 0.4% in men treated with raloxifene and decreased by 2.6 ± 0.7% in men who did not receive raloxifene (P < 0.001). Similar between-group differences were observed in the femoral neck (P = 0.06) and trochanter (P < 0.001). In men

receiving a GnRH agonist, raloxifene significantly increases bone mineral d. of the hip and tends to increase bone mineral d. of the spine.

IT **84449-90-1**, Raloxifene
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with **prostate** cancer)

RN 84449-90-1 HCAPLUS

CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



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L10 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:589254 HCAPLUS
DOCUMENT NUMBER: 141:134060
TITLE: Method of treatment of prostate cancer and composition for treatment thereof
INVENTOR(S): Castle, Erik P.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 5 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004142973	A1	20040722	US 2004-754308	20040109
WO 2004066962	A2	20040812	WO 2004-US668	20040112
WO 2004066962	A3	20041202		

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PRIORITY APPLN. INFO.: US 2003-440937P P 20030117
US 2004-754308 A 20040109

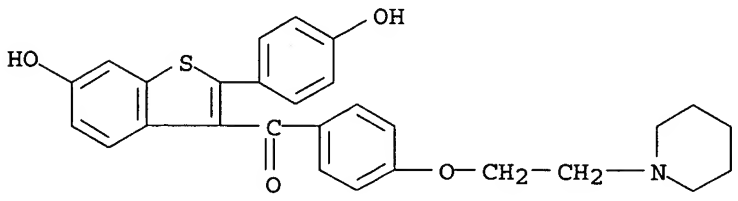
AB A method and composition for the treatment of prostate cancer comprises an effective amount of a nonsteroidal antiandrogen and an effective amount of a selective estrogen receptor modulator. The composition has fewer side effects such as breast tenderness and gynecomastia and also is more effective as an adjuvant therapy to prevent the reoccurrence of prostate cancer.

IT **84449-90-1**, Raloxifene
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(method of treatment of **prostate** cancer and composition for treatment thereof)

RN 84449-90-1 HCAPLUS

CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



L10 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:550743 HCAPLUS

DOCUMENT NUMBER: 141:82310

TITLE: Use of benzothiophenes and optional estrogen-lowering agents to treat and prevent prostate cancer

INVENTOR(S): Agus, David B.

PATENT ASSIGNEE(S): Cedars-Sinai Medical Center, USA

SOURCE: U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. Pat. Appl. 2002 198,235.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004132776	A1	20040708	US 2003-625152	20030723
US 2002198235	A1	20021226	US 2002-142087	20020509
WO 2005055922	A2	20050623	WO 2004-US23535	20040721

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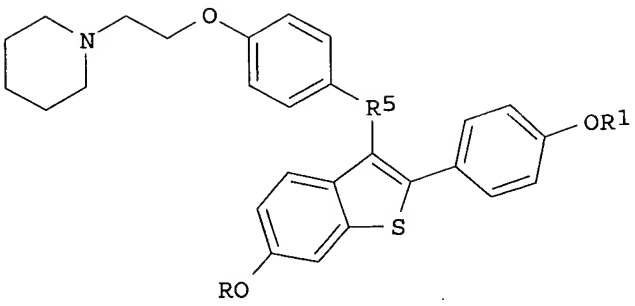
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2002-142087	A2	20020509
US 2001-290307P	P	20010510
US 2003-625152	A	20030723

OTHER SOURCE(S): MARPAT 141:82310

GI



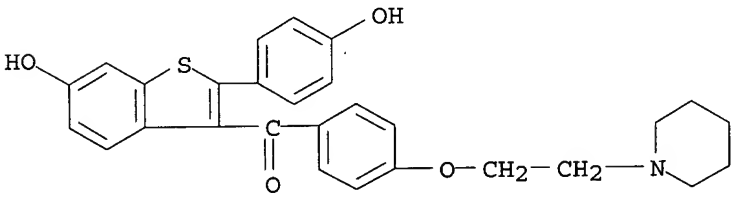
I

AB A method is disclosed for treating and preventing prostate cancer, particularly androgen-independent prostate cancer, the method including administering to a mammal a benzothiopene I (R, R1 = H, COR2, COR3, R4; R2 = H, C1-14 alkyl, C1-3 chloroalkyl, C1-3 fluoroalkyl, C5-7 cycloalkyl, C1-4 alkoxy, Ph; R3 = substituted Ph; R4 = C1-4 alkyl, C5-7 cycloalkyl, benzyl; R5 = O, C=O), or pharmaceutically acceptable salts or prodrugs thereof. The method may further include the administration of an estrogen-lowering drug to enhance efficacy of the compound of the invention.

IT **84449-90-1**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzothiophenes and optional estrogen-lowering agents for treatment and prevention of **prostate** cancer)

RN 84449-90-1 HCAPLUS

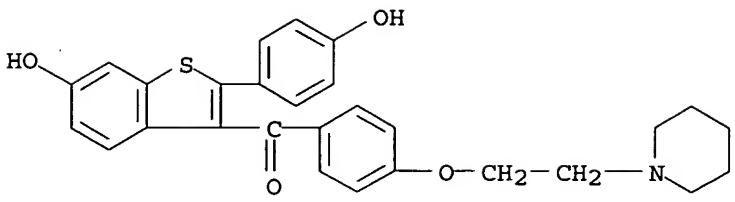
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



IT **82640-04-8**, Raloxifene hydrochloride **176672-18-7**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzothiophenes and optional estrogen-lowering agents for treatment and prevention of **prostate** cancer)

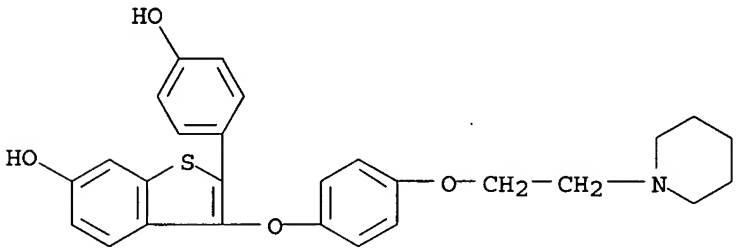
RN 82640-04-8 HCAPLUS

CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 176672-18-7 HCAPLUS
CN Benzo[b]thiophene-6-ol, 2-(4-hydroxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]- (9CI) (CA INDEX NAME)



L10 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:392335 HCAPLUS
DOCUMENT NUMBER: 140:386019
TITLE: Method using toremifene and related compounds for the treatment and chemoprevention of prostate cancer
INVENTOR(S): Steiner, Mitchell S.; Raghow, Sharan
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of U.S. Ser. No. 300,939.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004092602	A1	20040513	US 2003-611056		20030702
US 6265448	B1	20010724	US 1999-306958		19990507
EP 1475087	A2	20041110	EP 2004-18861		19990507
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, LT, LV, FI, RO, MK, CY, AL					
US 6413533	B1	20020702	US 2000-531472		20000320
US 6632447	B1	20031014	US 2000-707766		20001108
US 2003130316	A1	20030710	US 2002-300939		20021121
US 2004176470	A1	20040909	US 2003-747685		20031230
US 2004186185	A1	20040923	US 2003-747686		20031230
PRIORITY APPLN. INFO.:			US 1998-84602P	P	19980507
			US 1999-306958	A2	19990507

US 1999-436208	B2	19991108
US 2000-531472	A2	20000320
US 2000-707766	A2	20001108
US 2002-300939	A2	20021121
EP 1999-924157	A3	19990507
US 2000-660184	A2	20000912
US 2000-660191	A2	20000912
US 2000-660197	A2	20000912
US 2003-611056	A2	20030702

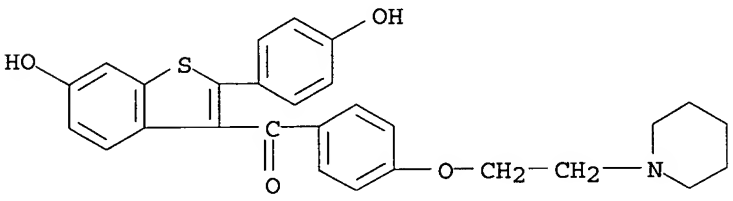
OTHER SOURCE(S): MARPAT 140:386019

AB Th invention relates to methods of treating a subject with pre-malignant lesions of prostate cancer, as well as methods of suppressing, inhibiting or reducing the incidence of pre-malignant lesions of prostate cancer. The methods of the invention use toremifene and related compds.

IT **84449-90-1**, Raloxifene
RL: PAC (Pharmacological activity); BIOL (Biological study)
(toremifene and related compds. for treatment and chemoprevention of **prostate** cancer)

RN 84449-90-1 HCAPLUS

CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



L10 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:810071 HCAPLUS

DOCUMENT NUMBER: 139:286332

TITLE: Method for chemoprevention of prostate cancer with selective estrogen receptor modulators

INVENTOR(S): Steiner, Mitchell S.; Raghow, Sharan

PATENT ASSIGNEE(S): The University of Tennessee Research Corporation, USA

SOURCE: U.S., 19 pp., Cont.-in-part of U.S. Ser. No. 660,184.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 10

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6632447	B1	20031014	US 2000-707766	20001108
US 6265448	B1	20010724	US 1999-306958	19990507
EP 1475087	A2	20041110	EP 2004-18861	19990507
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, LT, LV, FI, RO, MK, CY, AL				
US 6413533	B1	20020702	US 2000-531472	20000320
US 6410043	B1	20020625	US 2000-660191	20000912
US 6413534	B1	20020702	US 2000-660184	20000912
US 6413535	B1	20020702	US 2000-660197	20000912
US 2003130316	A1	20030710	US 2002-300939	20021121
US 2004092602	A1	20040513	US 2003-611056	20030702

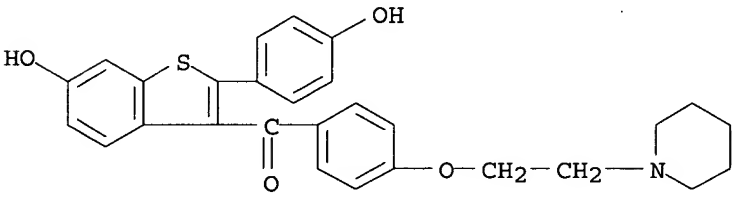
US 2004176470	A1	20040909	US 2003-747685	20031230
US 2004186185	A1	20040923	US 2003-747686	20031230
PRIORITY APPLN. INFO.:			US 1998-84602P	P 19980507
			US 1999-306958	A2 19990507
			US 1999-436208	A2 19991108
			US 2000-531472	A2 20000320
			US 2000-660184	A2 20000912
			US 2000-660191	A2 20000912
			US 2000-660197	A2 20000912
			EP 1999-924157	A3 19990507
			US 2000-707766	A1 20001108
			US 2002-300939	A2 20021121
			US 2003-611056	A2 20030702

AB This invention relates to the chemoprevention of prostate cancer and, more particularly, to a method of suppressing or inhibiting latent prostate cancer comprising administering to a mammalian subject a chemopreventive agent and analogs and metabolites thereof. The chemopreventive agent prevents, prevents recurrence of, suppresses or inhibit prostate carcinogenesis; and treats prostate cancer.

IT **84449-90-1**, Raloxifene
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chemoprevention of **prostate** cancer with selective estrogen receptor modulators)

RN 84449-90-1 HCAPLUS

CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 120 THERE ARE 120 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	2002:868735 HCAPLUS
DOCUMENT NUMBER:	137:363046
TITLE:	Use of benzothiophenes to treat and prevent prostate cancer
INVENTOR(S):	Agus, David
PATENT ASSIGNEE(S):	Cedars-Sinai Medical Center, USA
SOURCE:	PCT Int. Appl., 20 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	2

PATENT INFORMATION:

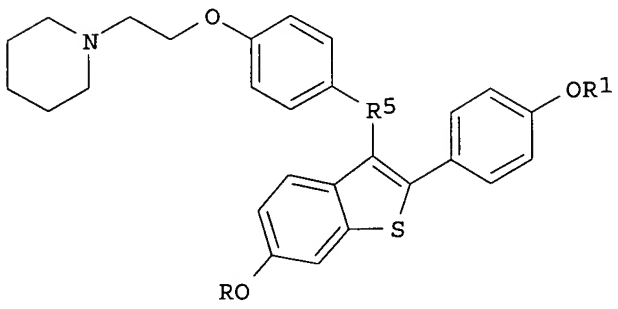
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002089801	A1	20021114	WO 2002-US14649	20020509

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,

CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1392304	A1	20040303	EP 2002-736702	20020509
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004529165	T2	20040924	JP 2002-586936	20020509
PRIORITY APPLN. INFO.:			US 2001-290307P	P 20010510
			WO 2002-US14649	W 20020509

OTHER SOURCE(S): MARPAT 137:363046
GI

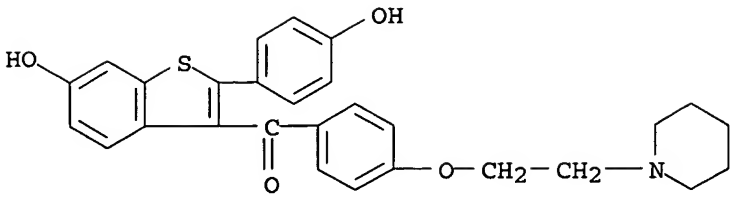


I

AB A method is disclosed for treating and preventing prostate cancer, the method comprising administering to a mammal a benzothiophene compound I [R, R1 = H, COR2, COR3, R4; R2 = H, C1-4 alkyl, C1-3 chloroalkyl, C1-3 fluoroalkyl, C5-7 cycloalkyl, C1-4 alkoxy, Ph; R3 = substituted Ph; R4 = C1-4 alkyl, C5-7 cycloalkyl, benzyl; R5 = O, C(=O)] or pharmaceutically acceptable salts thereof. Compds. of the invention include e.g. raloxifene.

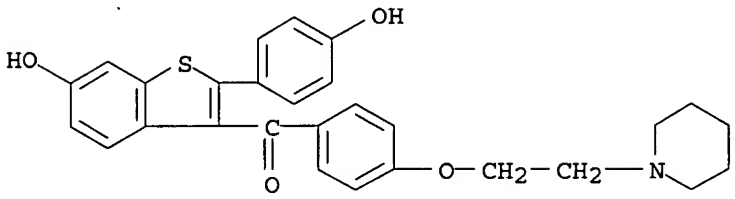
IT **82640-04-8**, Raloxifene hydrochloride **84449-90-1**, Raloxifene **84449-90-1D**, Raloxifene, prodrug derivs. **176672-18-7 176672-18-7D**, prodrug derivs. **182133-25-1**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzothiophene derivs. to treat and prevent **prostate** cancer)

RN 82640-04-8 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride (9CI) (CA INDEX NAME)

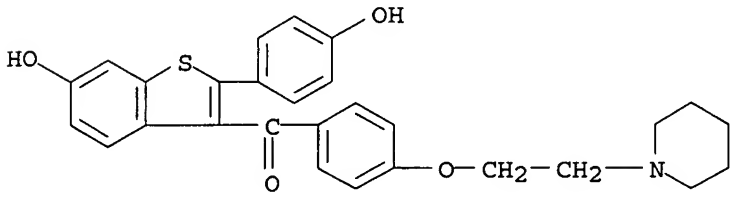


● HCl

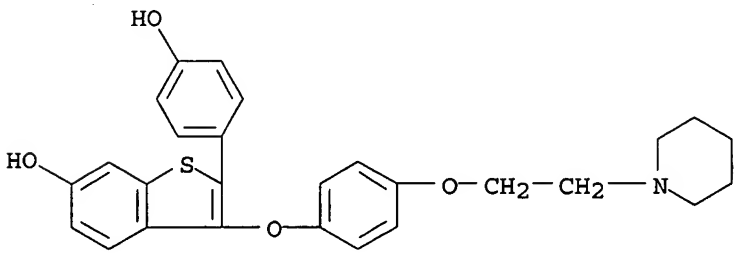
RN 84449-90-1 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 84449-90-1 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)

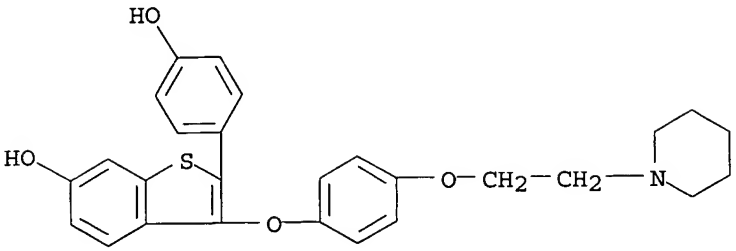


RN 176672-18-7 HCAPLUS
CN Benzo[b]thiophene-6-ol, 2-(4-hydroxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]- (9CI) (CA INDEX NAME)

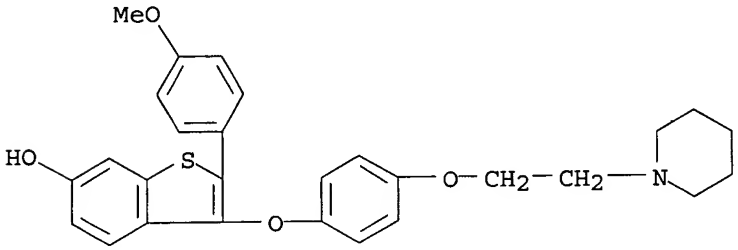


RN 176672-18-7 HCAPLUS
CN Benzo[b]thiophene-6-ol, 2-(4-hydroxyphenyl)-3-[4-[2-(1-

piperidinyl)ethoxy]phenoxy]- (9CI) (CA INDEX NAME)



RN 182133-25-1 HCAPLUS
CN Benzo[b]thiophene-6-ol, 2-(4-methoxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:728442 HCAPLUS
DOCUMENT NUMBER: 138:248094
TITLE: Raloxifene, a mixed estrogen agonist/antagonist, induces apoptosis in androgen-independent human prostate cancer cell lines
AUTHOR(S): Kim, Isaac Yi; Kim, Byung-Chul; Seong, Do Hwan; Lee, Dug Keun; Seo, Jeong-Meen; Hong, Young Jin; Kim, Heung-Tae; Morton, Ronald A.; Kim, Seong-Jin
CORPORATE SOURCE: Laboratory of Cell Regulation and Carcinogenesis, National Cancer Institute, Bethesda, MD, 20892, USA
SOURCE: Cancer Research (2002), 62(18), 5365-5369
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

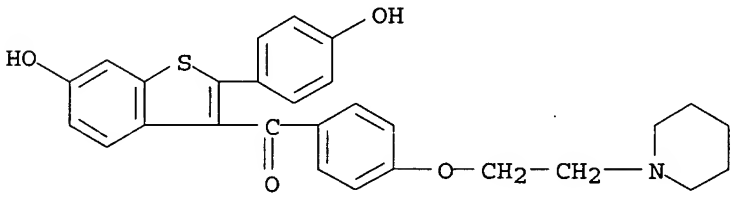
AB Raloxifene, a selective estrogen receptor (ER) modulator, is a mixed estrogen agonist/antagonist that was shown to prevent osteoporosis and breast cancer in women. Because the prostate contains high levels of ER-β, the present study investigated the effect of raloxifene in 3 well-characterized, androgen-independent human prostate cancer cell lines: (a) PC3; (b) PC3M; and (c) DU145. Reverse transcriptase-PCR and Western blot anal. for ER-α and ER-β demonstrated that all 3 cell lines express ER-β, whereas only PC3 and PC3M cells were pos. for ER-α. After the treatment with raloxifene, a dramatic increase in cell death was observed in a dose-dependent manner in the 3 prostate cancer cell lines (10-9 to 10-6 M range). Because the 3 prostate cancer cell

lines demonstrated similar morphol. changes after the raloxifene treatment, PC3 (ER-α/ER-β+) and DU145 (ER-β+ only) cells were selected to further characterize the raloxifene-induced cell death. Using the nucleus-specific stain 4',6-diamidino-2-phenylindole, nuclear fragmentation was observed in a time-dependent manner in both cell lines after exposure to 10-6 M raloxifene. Using the terminal deoxynucleotidyl transferase-mediated nick end labeling apoptotic assay, it was demonstrated that the nuclear fragmentation was caused by apoptosis. To investigate the possibility that caspase activation is involved in raloxifene-induced apoptosis, cells were treated with the pan-caspase inhibitor ZVAD. The results demonstrated that the dramatic change in cellular morphol. after treatment with raloxifene was no longer observed when cells were pretreated with ZVAD. Immunoblot demonstrated activation of caspases 8 and 9 in PC3 and DU145 cells, resp. Taken together, these results demonstrate that the mixed estrogen agonist/antagonist, raloxifene, induces apoptosis in androgen-independent human prostate cancer cell lines.

IT **84449-90-1**, Raloxifene
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(raloxifene induces apoptosis in androgen-independent human **prostate** cancer)

RN 84449-90-1 HCAPLUS

CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:519062 HCAPLUS

DOCUMENT NUMBER: 138:66287

TITLE: Raloxifene, a selective estrogen receptor modulator, induces apoptosis in androgen-responsive human prostate cancer cell line LNCaP through an androgen-independent pathway

AUTHOR(S): Kim, Isaac Yi; Seong, Do Hwan; Kim, Byung-Chul; Lee, Dug Keun; Remaley, Alan T.; Leach, Fredrick; Morton, Ronald A.; Kim, Seong-Jin

CORPORATE SOURCE: Laboratory of Cell Regulation and Carcinogenesis, National Cancer Institute, Bethesda, MD, 20892, USA

SOURCE: Cancer Research (2002), 62(13), 3649-3653
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

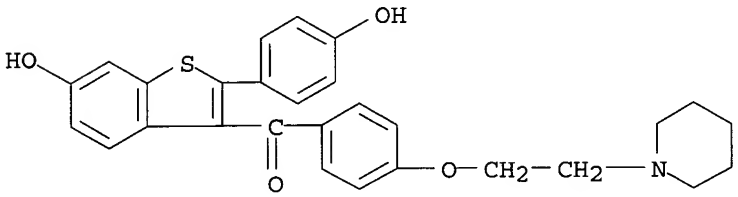
AB Raloxifene, a selective estrogen receptor (ER) modulator, is a mixed estrogen agonist/antagonist that has been shown to prevent osteoporosis and breast cancer in women. Because the prostate contains a high level of ER-β, the present study investigated the effect of raloxifene in the

androgen-sensitive human prostate cancer cell line LNCaP. Previously, it has been demonstrated that LNCaP cells express ER-β but not ER-α and that tamoxifen induces apoptosis in these cells. After treatment with raloxifene, a dramatic increase in cell death occurred in a dose-dependent manner (10-9 to 10-6 M range). Using the terminal deoxynucleotidyl transferase-mediated nick end labeling apoptotic assay, we demonstrated that the nuclear fragmentation was due to apoptosis. The dramatic change in cellular morphol. after treatment with raloxifene was no longer observed when cells were pretreated with a pan-caspase inhibitor, Z-VAD-FMK, and a specific caspase-9 inhibitor, Z-LEHD-FMK. Furthermore, immunoblot demonstrated an activation of caspase-9 in LNCaP cells. Because LNCaP cells contain a mutated androgen receptor that allows cellular proliferation in the presence of antiandrogens, prostate-specific antigen assay and transfection with a reporter construct containing luciferase gene under the control of androgen response element (pARE) were carried out. The results demonstrated that raloxifene does not significantly alter androgen receptor activity in LNCaP cells. Taken together, these results demonstrate that raloxifene, a selective ER modulator, induces apoptosis in the androgen-sensitive human prostate cancer cell line LNCaP through an androgen-independent pathway.

IT **84449-90-1**, Raloxifene
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(raloxifene induces apoptosis in androgen-responsive human **prostate** cancer cell line LNCaP through an androgen-independent pathway)

RN 84449-90-1 HCAPLUS

CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:635900 HCAPLUS
DOCUMENT NUMBER: 135:190841
TITLE: Method of treatment of prostate cancer and other cancers using androstenediols
INVENTOR(S): Loria, Roger M.
PATENT ASSIGNEE(S): Hollis-Eden Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001062259	A1	20010830	WO 2001-US6171	20010226

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2001041779	A5	20010903	AU 2001-41779		20010226
US 2001046980	A1	20011129	US 2001-794531		20010226
PRIORITY APPLN. INFO.:			US 2000-185115P	P	20000225
			WO 2001-US6171	W	20010226

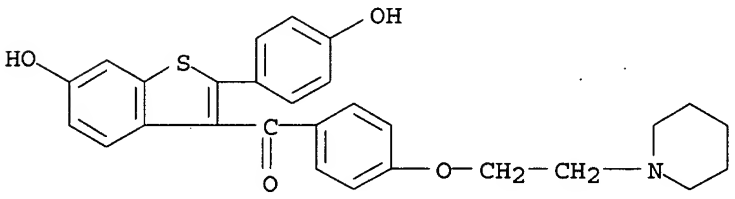
OTHER SOURCE(S): MARPAT 135:190841

AB The present invention relates to the field of cancer, and in particular hormone dependent cancers including, but not limited to prostate, breast, endometrial, ovarian, thyroid, bone, and testis. The present invention also relates to the use of steroid analogs, and in particular analogs of Δ5-androstene-3-β,17α-diol, and its epimer Δ5-androstene-3-β,17β-diol for the treatment and prevention of cancer. Drug formulations containing the analogs are exemplified as is the use of the analogs in treatment.

IT **84449-90-1**, Raloxifene
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of treatment of **prostate** cancer and other cancers using androstenediols in combination with other drugs)

RN 84449-90-1 HCAPLUS

CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	2001:359767 HCAPLUS
DOCUMENT NUMBER:	134:348253
TITLE:	A method for chemoprevention of prostate cancer
INVENTOR(S):	Steiner, Mitchell S.; Raghow, Sharan
PATENT ASSIGNEE(S):	The University of Tennessee Research Corporation, USA
SOURCE:	PCT Int. Appl., 41 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	10
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

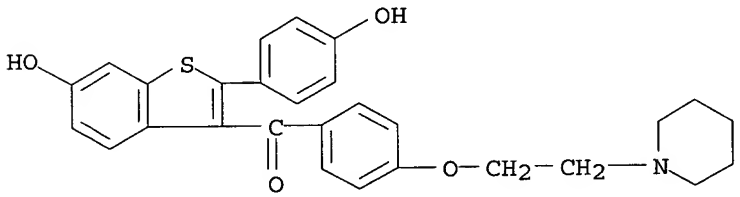
WO 2001034117	A1	20010517	WO 2000-US30658		20001108
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
US 6413533	B1	20020702	US 2000-531472		20000320
CA 2390295	AA	20010517	CA 2000-2390295		20001108
EP 1229903	A1	20020814	EP 2000-978418		20001108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2003513903	T2	20030415	JP 2001-536117		20001108
NO 2002002221	A	20020628	NO 2002-2221		20020508
BG 106738	A	20030228	BG 2002-106738		20020522
PRIORITY APPLN. INFO.:			US 1999-436208	A	19991108
			US 2000-531472	A	20000320
			US 1998-84602P	P	19980507
			US 1999-306958	A2	19990507
			WO 2000-US30658	W	20001108

AB This invention relates to the chemoprevention of prostate cancer and, more particularly, to a method of suppressing or inhibiting latent prostate cancer comprising administering to a mammalian subject a chemopreventive agent, e.g. an antiestrogen or analog or metabolite thereof. The chemopreventive agent prevents, prevents recurrence of, suppresses or inhibits prostate carcinogenesis; and treats prostate cancer. An animal model of prostate cancer is described; the model was used to assess the effects of toremifene.

IT **84449-90-1**, Raloxifene
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**prostate** cancer chemoprevention)

RN 84449-90-1 HCAPLUS

CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:811500 HCAPLUS
DOCUMENT NUMBER: 132:44984
TITLE: Pharmaceutical combinations for the compensation of a testosterone deficiency in man with simultaneous protection of the prostate
INVENTOR(S): Hubler, Doris; Oettel, Michael; Sobek, Lothar; Elger,

Walter; Al-Mudhaffar, Abdul-Abbas
PATENT ASSIGNEE(S): Jenapharm G.m.b.H. und Co. K.-G., Germany
SOURCE: Ger. Offen., 8 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19825591	A1	19991223	DE 1998-19825591	19980609
WO 9965228	A2	19991216	WO 1999-DE1652	19990607
WO 9965228	A3	20000914		
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RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1084569	A2	20010321	EP 1999-938132	19990607
EP 1084569	B1	20030305		
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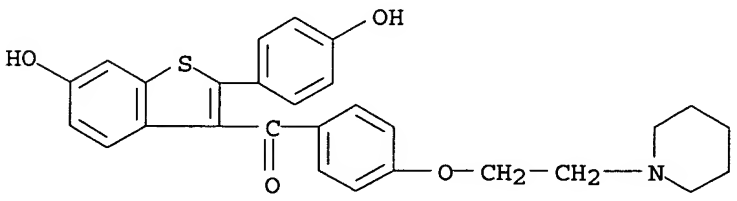
JP 2002518294	T2	20020625	JP 2000-554127	19990607
JP 3645489	B2	20050511		
AT 233976	E	20030315	AT 1999-938132	19990607
PT 1084569	T	20030731	PT 1999-938132	19990607
ES 2194495	T3	20031116	ES 1999-938132	19990607

PRIORITY APPLN. INFO.: DE 1998-19825591 A 19980609
WO 1999-DE1652 W 19990607

AB Pharmaceutical combinations are provided which compensate an absolute or relative testosterone deficit with simultaneous prophylaxis against formation of benign prostatic hyperplasia or prostate carcinoma. The combinations of the invention contain a natural or synthetic androgen in combination with a gestagen, an antigestagen, an antiestrogen, a gonadotropin-releasing hormone analog, a testosterone-5α-reductase inhibitor, an α-adrenoceptor blocker, or a phosphodiesterase inhibitor. In comparison with the combinations of the invention, the substances alone do not have the desired effect.

IT **84449-90-1**, Raloxifene
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical combinations for compensation of testosterone deficiency with simultaneous protection of **prostate**)

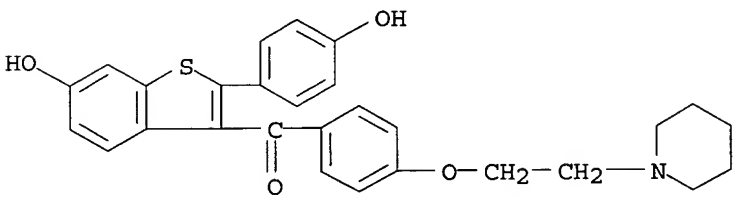
RN 84449-90-1 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



L10 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:491610 HCAPLUS
DOCUMENT NUMBER: 113:91610
TITLE: Inhibition of experimentally induced mouse prostatic hyperplasia by castration or steroid antagonist administration
AUTHOR(S): Sikes, Robert A.; Thomsen, Sharon; Petrow, Vladimir; Neubauer, Blake L.; Chung, Leland W. K.
CORPORATE SOURCE: M.D. Anderson Cancer Cent., Univ. Texas, Houston, TX, 77030, USA
SOURCE: Biology of Reproduction (1990), 43(2), 353-62
CODEN: BIREBV; ISSN: 0006-3363
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mouse prostatic hyperplasia has been induced exptl. by implanting fetal urogenital sinus tissue into the prostate gland of syngeneic mice. The effects of castration and steroid antagonist administration on the growth of the prostate gland during both the early (15 days) and late (30 days) phases of prostatic enlargement were compared. Castration at the time of induction of prostatic hyperplasia is by far the most effective method of inhibiting prostatic overgrowth. A comparison of castration for 7 days with the short-term (7 days) administration of steroid antagonists showed that during the early phase of prostatic enlargement castration is more effective than antiandrogen (cyproterone) which is more effective than 5α-reductase inhibitors (17β-N,N-diethylcarbamoyl-4-methyl-4-aza-5α-androstan-3-one and 6-methylene-4-pregnene-3,20-dione). In the late phase of mouse prostatic enlargement, castration for 7 days is less effective than treatment with either antiandrogen or a 5α-reductase inhibitor. The data indicate that treatment with a combination of an antiestrogen (keoxifene) with a 5α-reductase inhibitor (in particular, 6-methylene progesterone) is the most effective combination for reducing prostatic overgrowth. The antiestrogen (keoxifene) treatment alone was ineffective in both the early and late phases of prostatic overgrowth.

IT **84449-90-1**, Keoxifene
RL: BIOL (Biological study)
(**prostate** gland hyperplasia inhibition by castration and)
RN 84449-90-1 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



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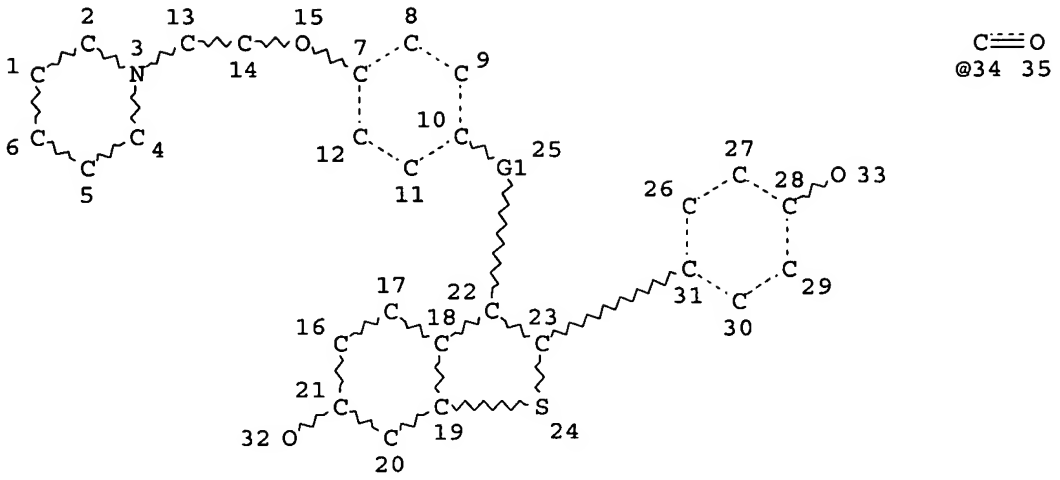

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DEFAULT ECLEVEL IS LIMITED

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NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE
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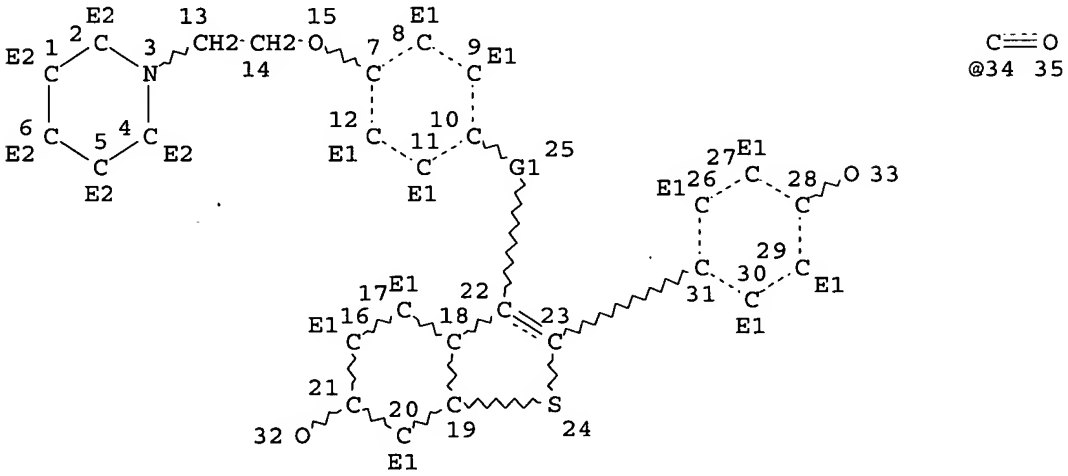
L6 STR



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NUMBER OF NODES IS  35

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L10          16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8(L)L9
L11           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8(L)PRODRUG
L12           3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11 NOT L10


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L12  ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:423722  HCAPLUS
DOCUMENT NUMBER:          142:469160
TITLE:                    pH sensitive prodrugs of 2,6-diisopropylphenol
INVENTOR(S):              Marappan, Subramanian; Davenport, Cris; Sarshar,
                          Sepehr
PATENT ASSIGNEE(S):       Auspex Pharmaceuticals, Inc., USA
SOURCE:                   PCT Int. Appl., 61 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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     WO 2005044201         A2    20050519    WO 2004-US7935          20040315
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
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             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
             BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
             ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
             SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
             TD, TG
PRIORITY APPLN. INFO.:                       US 2003-514340P     P  20031024
AB   The present invention is directed to water-soluble derivs. of
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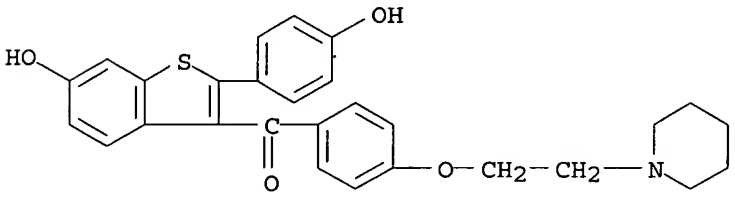
2,6-diisopropylphenol (propofol). The compds. act as prodrugs of 2,6-diisopropylphenol and metabolize rapidly to propofol thereby providing an alternative to the water-insol. 2,6-diisopropylphenol. Pharmaceutical compns. comprising these compds., methods of induction and maintenance of anesthesia or sedation as well as methods of treating neurodegenerative diseases utilizing pharmaceutical compns. comprising these compds. and methods of preparing them are also disclosed. N-(2-Piperidin-1-yl-ethyl)-succinamic acid 2,6-diisopropylphenyl ester was obtained by the reaction of propofol hemisuccinate with 1-(2-aminoethyl)pyrrolidine, then it was reacted with HCl to obtain hydrochloride salt (I). Efficacy of I at 150 mg/kg in induction of anesthesia in mice are shown.

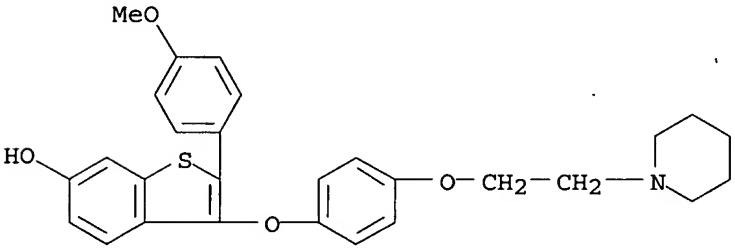
IT **82640-04-8**, Evista **182133-25-1**, Arzoxifene
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pH sensitive **prodrugs** of diisopropylphenol)

RN 82640-04-8 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 182133-25-1 HCAPLUS
CN Benzo[b]thiophene-6-ol, 2-(4-methoxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]- (9CI) (CA INDEX NAME)

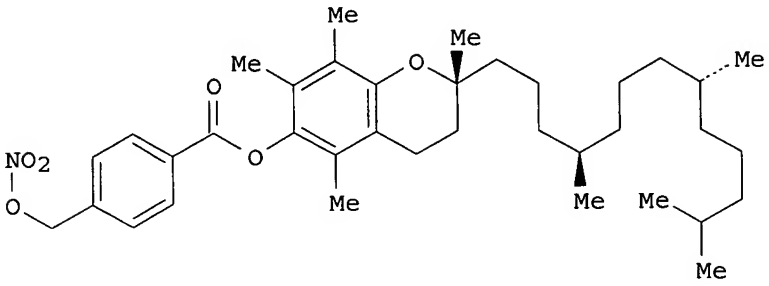


L12 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:652131 HCAPLUS
DOCUMENT NUMBER: 139:214237
TITLE: Preparation of nitrate prodrugs able to release nitric oxide in a controlled and selective way and their use for prevention and treatment of inflammatory, ischemic and proliferative diseases
INVENTOR(S): Scaramuzzino, Giovanni
PATENT ASSIGNEE(S): Italy
SOURCE: Eur. Pat. Appl., 313 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1336602	A1	20030820	EP 2002-425075	20020213
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRIORITY APPLN. INFO.:			EP 2002-425075	20020213

GI



II

AB New pharmaceutical compds. of general formula F-(X)q (I) [q = 1-5, preferably 1; F is chosen among drugs such as δ-tocopherol, clidanac, diethylhomospermine, glucosamine, thymocartin, vofopitant, etc.; X is chosen among 4 groups M, T, V, and Y where M = ONO2, nitrate salt, nitrite ester, ONO, thoinitrite, SNO, etc., T = OR1-M, OR1OR1-M, SR1NR2R1-M, NR2R1-M, NR2R1SR1-M, etc., R1 = saturated or unsatd., linear or branched alkylene, having 1 to 21 carbon atoms or a saturated or unsatd., optionally heterosubstituted or branched cycloalkylene, having 3 to 7 carbon atoms or an optionally heterosubstituted arylene having 3 to 7 carbon atoms; R2 = H, saturated or unsatd., linear or branched 1-21 carbon atom alkyl, saturated or unsatd. optionally heterosubstituted or branched 3-7 carbon cycloalkyl, optionally heterosubstituted 3-7 carbon aryl; R1, R2 = OH, SH, F, Cl, Br, OPO3H2, CO2H, etc.; bond between F and T = carboxylic ester, carboxylic amide, glycoside, azo, thioester, sulfonic ester, etc.; V = Z-M2, OZ-M2, NR2Z-M2, R1Z-M2, OR1-M2, OR1Z-M2, M2 = M, R1-M, OR1-M, SR1-M, NR2R1-M; ZM2 = COCH2CH(M2)CH2N+Me3, COCH2CH2COM2, COCH(NHR2)CH2M2, etc.; Y = 4-COC6H4CH2ONO2, O(CH2)4ONO2, COCH(NH2)CH2ONO2, 3-OC6H4CH2ONO2, etc.] were prepared For example, α-tocopherol reacted with 4-HO2CC6H4CH2ONO2 to give the nitroxymethyl derivative II. The compds. of general formula I are nitrate prodrugs which can release nitric oxide in vivo in a controlled and selective way and without hypotensive side effects and for this reason they are useful for the preparation of medicines for prevention and treatment of inflammatory, ischemic, degenerative and proliferative diseases of musculoskeletal, tegumental, respiratory, gastrointestinal, genito-urinary and central nervous systems.

IT **586348-51-8P 586348-52-9P 586348-55-2P**
586348-57-4P 586348-59-6P 586348-61-0P
586348-62-1P 586348-63-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of nitrate **prodrugs** for treating or preventing inflammatory, ischemic, degenerative, and proliferative diseases)

RN 586348-51-8 HCAPLUS
CN Butanoic acid, 4-(nitrooxy)-, 2-(4-hydroxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]benzoyl]benzo[b]thien-6-yl ester, nitrate (salt) (9CI) (CA INDEX NAME)

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CRN 586348-50-7
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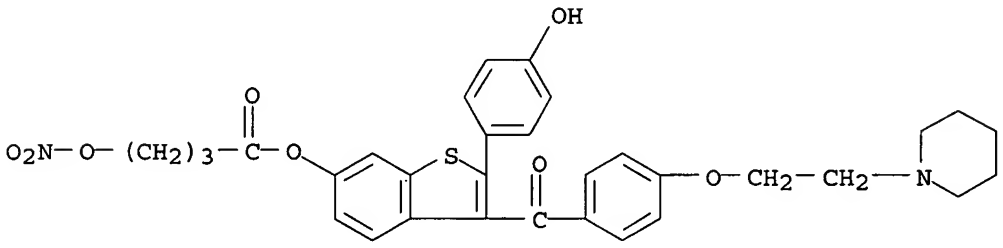

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CRN 7697-37-2
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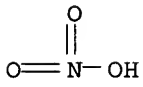

RN 586348-52-9 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-, nitrate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 84449-90-1
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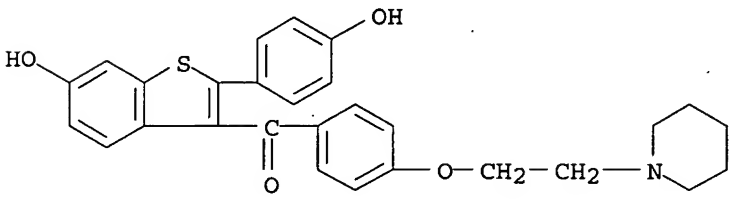

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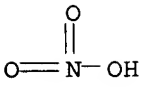
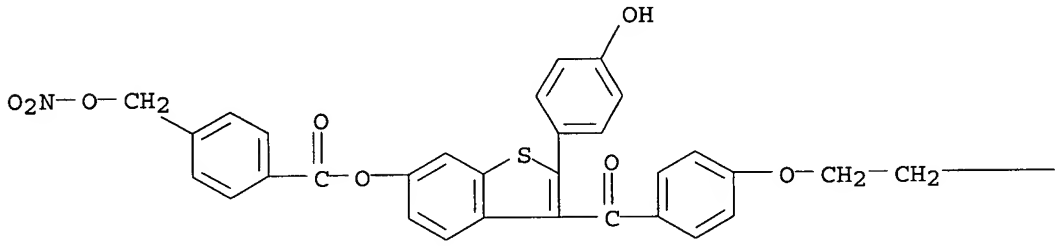


RN 586348-55-2 HCAPLUS
CN Benzoic acid, 4-[(nitrooxy)methyl]-, 2-(4-hydroxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]benzoyl]benzo[b]thien-6-yl ester, nitrate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 586348-54-1
CMF C36 H32 N2 O8 S

PAGE 1-A



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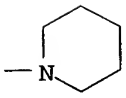

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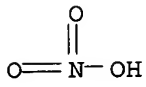
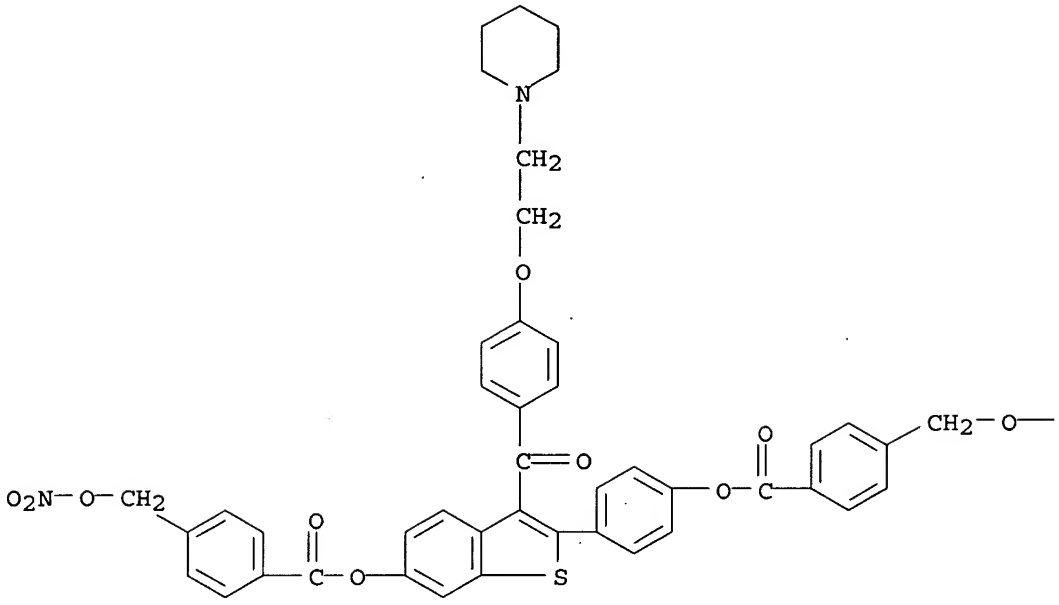


RN 586348-57-4 HCAPLUS
CN Benzoic acid, 4-[(nitrooxy)methyl]-, 2-[4-[[4-[(nitrooxy)methyl]benzoyl]oxy]phenyl]-3-[4-[2-(1-piperidinyl)ethoxy]benzoyl]benzo[b]thien-6-yl ester, mononitrate (9CI) (CA INDEX NAME)

CM 1

CRN 586348-56-3
CMF C44 H37 N3 O12 S

PAGE 1-A

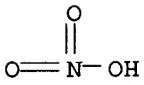


PAGE 1-B

—NO_2

CM 2

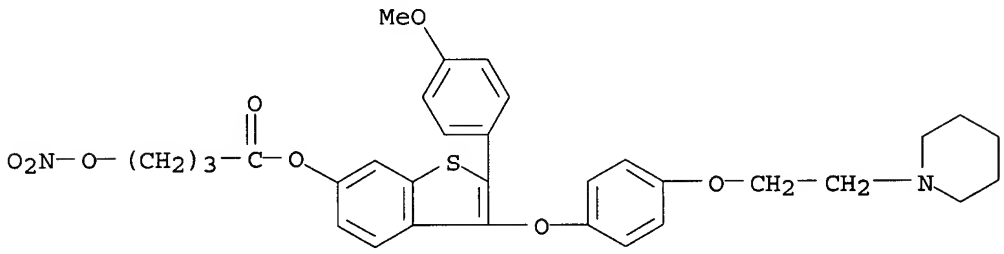
CRN 7697-37-2
CMF H N O3



RN 586348-59-6 HCAPLUS
CN Butanoic acid, 4-(nitrooxy)-, 2-(4-methoxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]benzo[b]thien-6-yl ester, nitrate (9CI) (CA INDEX NAME)

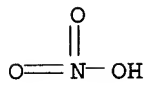
CM 1

CRN 586348-58-5
CMF C32 H34 N2 O8 S



CM 2

CRN 7697-37-2
CMF H N O3

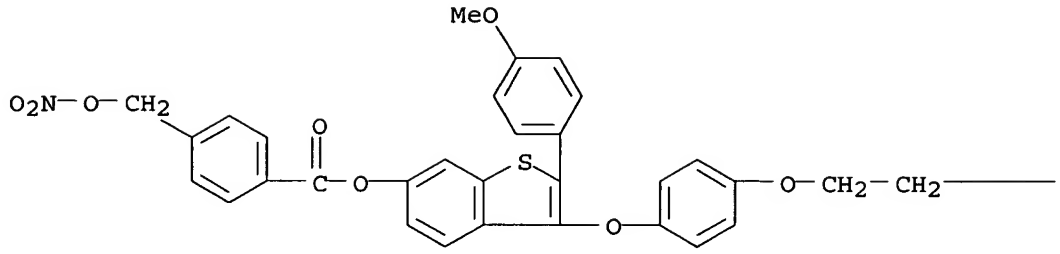


RN 586348-61-0 HCAPLUS
CN Benzoic acid, 4-[(nitrooxy)methyl]-, 2-(4-methoxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]benzo[b]thien-6-yl ester, nitrate (9CI) (CA INDEX NAME)

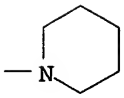
CM 1

CRN 586348-60-9
CMF C36 H34 N2 O8 S

PAGE 1-A



PAGE 1-B



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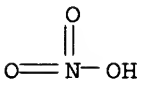
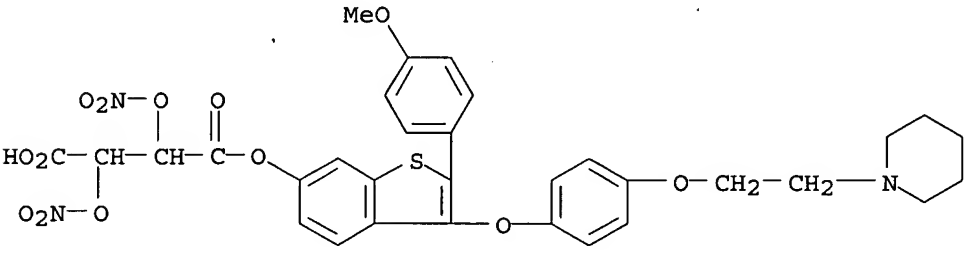
CRN 7697-37-2
CMF H N O3



RN 586348-62-1 HCAPLUS
CN Butanedioic acid, 2,3-bis(nitrooxy)-, mono[2-(4-methoxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]benzo[b]thien-6-yl] ester (9CI) (CA INDEX NAME)



RN 586348-63-2 HCAPLUS
CN Benzo[b]thiophene-6-ol, 2-(4-methoxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-, nitrate (salt) (9CI) (CA INDEX NAME)

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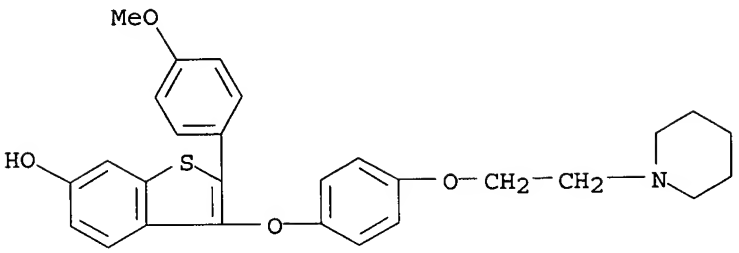
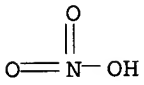
CRN 182133-25-1
CMF C28 H29 N O4 S



CM 2

CRN 7697-37-2
CMF H N O3



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:798040 HCAPLUS
DOCUMENT NUMBER: 135:339222
TITLE: Inhibition of abnormal cell proliferation with camptothecin or a derivative, analog, metabolite, or prodrug thereof, and combinations including camptothecin
INVENTOR(S): Rubinfeld, Joseph
PATENT ASSIGNEE(S): Supergen, Inc., USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001080843	A2	20011101	WO 2001-US12848	20010419
WO 2001080843	A3	20020815		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6420378	B1	20020716	US 2000-553710	20000420

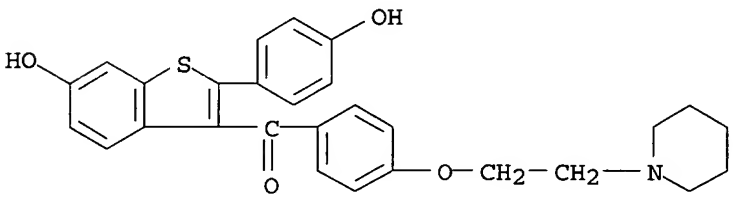
CA 2404970 AA 20011101 CA 2001-2404970 20010419
EP 1276479 A2 20030122 EP 2001-930607 20010419
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.: US 2000-553710 A1 20000420
US 1999-418862 A2 19991015
WO 2001-US12848 W 20010419

AB A method for treating diseases associated with abnormal cell proliferation comprises delivering to a patient in need of treatment a compound selected from 20(S)-comptothecin, an analog of 20(S)-comptothecin, a derivative of 20(S)-camptothecin, a prodrug of 20(S)-camptothecin, and pharmaceutically active metabolite of 20(S)-camptothecin, in combination with an effective amount of one or more agents selected form the group consisting of alkylating agent, antibiotic agent, antimetabolic agent, hormonal agent, plant-derived agent, anti-angiogenesis agent and biol. agent. The method can be used to treat benign tumors, malignant or metastatic tumors, leukemia and diseases associated with abnormal angiogenesis.

IT **84449-90-1**, Raloxifene
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(camptothecin or derivative, analog, metabolite, or **prodrug** thereof for inhibition of abnormal cell proliferation, and combinations including camptothecin)

RN 84449-90-1 HCAPLUS

CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



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L9 42118 SEA FILE=HCAPLUS ABB=ON PLU=ON ("PROSTATE CANCER"/CV OR "PROSTATE GLAND, NEOPLASM"/CV) OR PROSTATE?
L31 5840 SEA FILE=HCAPLUS ABB=ON PLU=ON L9(L)(?DRUG? OR ?PHARMA? OR ?MEDICIN? OR CHEMOPREVENT?)
L33 2151 SEA FILE=HCAPLUS ABB=ON PLU=ON ANDROGEN(W)DEPENDENT
L35 168 SEA FILE=HCAPLUS ABB=ON PLU=ON L33 AND L31
L36 71 SEA FILE=HCAPLUS ABB=ON PLU=ON L35 AND ANDROGEN(W)INDEPENDENT

L37 5 SEA FILE=HCAPLUS ABB=ON PLU=ON L36 AND PRODRUG

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L37 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:251615 HCAPLUS
DOCUMENT NUMBER: 139:128686
TITLE: Development of a prostate-specific promoter for gene therapy against **androgen-independent** prostate cancer
AUTHOR(S): Furuhata, Souichi; Ide, Hisamitsu; Miura, Yoshiaki; Yoshida, Teruhiko; Aoki, Kazunori
CORPORATE SOURCE: Genetics Division, National Cancer Center Res. Inst., Tokyo, 104-0045, Japan
SOURCE: Molecular Therapy (2003), 7(3), 366-374
CODEN: MTOHCK; ISSN: 1525-0016
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Androgen ablation has been the standard treatment for metastasized **prostate** cancer. In most cases, however, **prostate** cancer cells eventually lose androgen dependency and become refractory to the conventional endocrine therapy. **Androgen-independent** **prostate** cancer is characterized by a heterogeneous loss of androgen receptor (AR) expression among tumor cells. **Prostate** -specific promoters such as **prostate**-specific antigen and rat probasin (rPB) promoters have been examined in the development of gene therapy targeted to **prostate** cancer. However, those promoters require binding of the androgen-AR complex to the androgen-response element and are active only in the **androgen-dependent** **prostate** cancer cell lines and not in the **androgen-independent** cell lines. To target transgene expression in **androgen-independent prostate** cancer, we designed a **prostate**-specific promoter that is activated by the retinoids-retinoid receptor complex instead of the androgen-AR complex. The modified rPB promoters expressed transgenes in response to retinoid in both **androgen-dependent** and **androgen-independent prostate** cancer cells and not in other cancer cell lines or in human normal cells, in vitro and in vivo. Furthermore, the combination of retinoid treatment and adenovirus-mediated gene transfer of the modified rPB-driven HSV-tk gene resulted in a significant growth suppression of the **androgen-independent prostate** cancer cells in the presence of the **prodrug** ganciclovir. This study suggests that tailoring of the hormone-responsive elements may offer a new therapeutic opportunity against the hormone-refractory stage of **prostate** cancer.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:340548 HCAPLUS
DOCUMENT NUMBER: 137:304376
TITLE: Transcription-targeted gene therapy for **androgen-independent** prostate cancer
AUTHOR(S): Martiniello-Wilks, Rosetta; Tsatralis, Tania; Russell, Peter; Brookes, Diana E.; Zandvliet, Dorethea; Lockett, Linda J.; Both, Gerald W.; Molloy, Peter L.; Russell, Pamela J.
CORPORATE SOURCE: Oncology Research Centre, Prince of Wales Hospital, Randwick, 2031, Australia
SOURCE: Cancer Gene Therapy (2002), 9(5), 443-452
CODEN: CGTHEG; ISSN: 0929-1903

PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Escherichia coli enzyme (purine nucleoside phosphorylase, PNP) gene is delivered directly into PC3 tumors by one injection of replication-deficient human type-5 adenovirus (Ad5). Expressed PNP converts the systemically administered **prodrug**, 6MPDR, to a toxic purine, 6MP, causing cell death. We sought to increase the specificity of recombinant Ad vectors by controlling PNP expression with the promoter region from the **androgen-dependent**, **prostate**-specific rat probasin (Pb) gene. To increase its activity, the promoter was combined with the SV40 enhancer (SVPb). Cell lines were transfected with plasmids containing both a reporter gene, under SVPb control, and a reference gene cassette to allow normalization of expression levels. Plasmids expressed .apprx.20-fold more reporter in **prostate** cancer than in other cells, but surprisingly, the SVPb element was both **androgen-independent** and retained substantial **prostate** specificity. Killing by Ad5-SVPb-PNP vector of cell lines cultured with 6MPDR for 6 days was 5- to 10-fold greater in **prostate** cancer than in liver or lung cells. In vivo, a single intratumoral injection of Ad5-SVPb-PNP (4+108 pfu), followed by 6MPDR administration twice daily for 6 days, significantly suppressed the growth of human **prostate** tumors in nude mice and increased their survival compared to control animals. Thus, the **androgen-independent**, **prostate**-targeting Ad5 vector reduces human **prostate** cancer growth significantly in vitro and in vivo. This first example of an **androgen-independent** vector points the way toward treatment of emerging **androgen-independent prostate** cancer in conjunction with hormone ablation therapy at a time when the tumor burden is low.
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:738485 HCAPLUS
DOCUMENT NUMBER: 134:260965
TITLE: Tributyrin induces differentiation, growth arrest and apoptosis in androgen-sensitive and androgen-resistant human prostate cancer cell lines
AUTHOR(S): Maler, Simone; Reich, Ella; Martin, Renate; Bachem, Max; Altug, Vedat; Hautmann, Richard E.; Gschwend, Jurgen E.
CORPORATE SOURCE: Department of Urology, University of Ulm, Ulm, D-89075, Germany
SOURCE: International Journal of Cancer (2000), 88(2), 245-251
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This work investigated the potency of tributyrin, an orally available **prodrug** of butyrate, to induce growth arrest, differentiation and apoptosis in LNCaP (**androgen-dependent**) and PC-3 and TSU-PRI (**androgen-independent**) human **prostate** cancer cell lines. The cells were treated with 0.1-5 mM tributyrin or sodium butyrate. Both agents induced a more differentiated, fibroblast-like phenotype in androgen-sensitive as well as androgen-resistant cell lines. Expression of **prostate**-specific antigen (an indicator of differentiation) was increased in LNCaP cells by tributyrin. The IC50 for sodium butyrate was 2.5 mM in PC-3 and TSU-PRI

cells. LNCaP cells exhibited <50% growth inhibition at 5 mM sodium butyrate. However, the IC50 for tributyrin was 0.8 mM in PC-3 cells, 1.2 mM in TSU-PRI cells and 3.1 mM in LNCaP cells. Flow cytometry revealed a strong G1 phase arrest after exposure to tributyrin or sodium butyrate. Both agents greatly increased the degree of apoptosis, compared with mock-treated cells. Overall, tributyrin had a 2.5-3-fold growth-inhibitory and apoptosis-inducing potency compared with equimolar concns. of sodium butyrate. Tributyrin is more potent than butyrate with regard to cell growth inhibition and apoptosis induction at **pharmacol.** relevant concns. Hence, tributyrin may be a promising candidate for clin. protocols in **prostate** cancer.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:384381 HCAPLUS
DOCUMENT NUMBER: 133:42165
TITLE: Prostate stem cell antigen (PSCA) and its diagnostic and immunotherapeutic uses
INVENTOR(S): Reiter, Robert; Witte, Owen
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 171 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000032752	A1	20000608	WO 1999-US28883	19991202
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6258939	B1	20010710	US 1998-203939	19981202
US 6261789	B1	20010717	US 1999-251835	19990217
US 6261791	B1	20010717	US 1999-318503	19990525
CA 2351887	AA	20000608	CA 1999-2351887	19991202
AU 2000021668	A5	20000619	AU 2000-21668	19991202
AU 771026	B2	20040311		
EP 1135467	A1	20010926	EP 1999-966018	19991202
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002531082	T2	20020924	JP 2000-585383	19991202
AU 766669	B2	20031023	AU 2001-97137	20011207
PRIORITY APPLN. INFO.:			US 1998-203939 A	19981202
			US 1999-251835 A	19990217
			US 1999-318503 A	19990525
			US 1997-814279 B2	19970310
			US 1998-71141P P	19980112
			US 1998-74675P P	19980213
			AU 1998-65481 A0	19980310
			US 1998-38261 A2	19980310
			WO 1999-US28883 W	19991202

AB The invention provides a novel prostate cell-surface antigen, designated Prostate Stem Cell Antigen (PSCA), which is widely over-expressed across all stages of prostate cancer, including high grade prostatic intraepithelial neoplasia (PIN), **androgen-dependent** and **androgen-independent** prostate tumors. The PSCA gene shows 30% homol. to stem cell antigen-2 (SCA-2), a member of the

Thy-1/Ly-6 family of glycosylphosphatidylinositol (GPI)-anchored cell surface antigens, and encodes a 123-amino acid protein with an N-terminal signal sequence, a C-terminal GPI-anchoring sequence, and multiple N-glycosylation sites. PSCA mRNA expression is highly upregulated in both **androgen-dependent** and **androgen-independent** prostate cancer xenografts. In situ mRNA anal. localizes PSCA expression to the basal cell epithelium, the putative stem cell compartment of the prostate. Flow cytometric anal. demonstrates that PSCA is expressed predominantly on the cell surface and is anchored by a GPI linkage. Fluorescent in situ hybridization anal. localizes the PSCA gene to chromosome 8q24.2, a region of allelic gain in >80% of prostate cancers. PSCA may be an optimal therapeutic target in view of its cell surface location, and greatly upregulated expression in certain types of cancer such as prostate cancer cells. The invention also provides antibodies to PSCA, which can be used therapeutically to destroy such prostate cancer cells. In addition, PSCA proteins and PSCA-encoding nucleic acid mols. may be used in various immunotherapeutic methods to promote immune-mediated destruction of prostate tumors. Further, methods of detection/diagnosis and treatment, as well as a transgenic animal are provided.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:297214 HCAPLUS

DOCUMENT NUMBER: 133:202714

TITLE: Adenovirus-mediated suicide-gene therapy using the herpes simplex virus thymidine kinase gene in cell and animal models of human prostate cancer: changes in tumor cell proliferative activity

AUTHOR(S): Cheon, J.; Kim, H. K.; Moon, D. G.; Yoon, D. K.; Cho, J. H.; Koh, S. K.

CORPORATE SOURCE: Department of Urology, Korea University Hospital, Seoul, S. Korea

SOURCE: BJU International (2000), 85(6), 759-766
CODEN: BJINFO; ISSN: 1464-4096

PUBLISHER: Blackwell Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Objectives: To determine the feasibility and efficacy of suicide-gene therapy using adenovirus (Ad)-mediated herpes simplex virus thymidine kinase (HSV-TK) and the **prodrug** acyclovir, and to evaluate changes in the biol. phenotype for tumor cell proliferative activity after suicide-gene therapy in animal models of human **prostate** cancer. Materials and methods: Using a replication-defective adenoviral vector (cytomegalovirus, CMV) containing the β-galactosidase gene (Ad-CMV-β-gal) as a control and Ad-CMV-TK as the therapeutic vector under the transcriptional control of the CMV promoter, transduction efficiency was assessed in vitro by infecting LNCaP and PC-3 **androgen-dependent** and independent human **prostate** cancer cells with Ad-CMV-β-gal, and using X-gal staining. The TK activity in **prostate** cancer cells infected with Ad-CMV-TK was determined by measuring TK-mediated [3H]-gancyclovir phosphorylation. The sensitivity of LNCaP and PC-3 cells to Ad-CMV-TK in vitro was determined after infection with the therapeutic vector with or without acyclovir. The inhibition of PC-3 tumor growth in vivo induced by the Ad-CMV-TK/acyclovir suicide-gene system was assessed in sep. and controlled expts. using human **prostate** cancer mouse models. Ki-67 proliferative antigen and proliferating cell nuclear antigen (PCNA), both useful proliferative indexes, were evaluated using immunohistochem.

staining (MIB-1 monoclonal antibody and monoclonal anti-PCNA antibody) in formalin-fixed, paraffin-embedded tissues from gene therapy-treated and control animals. Results: The mean TK activity was significantly higher in LNCaP and PC-3 cells infected with Ad-CMV-TK than in cells infected with Ad-CMV-β-gal, used as a control (P<0.05). The growth of human **prostate** cancer cells with Ad-CMV-TK was significantly inhibited by adding acyclovir in vitro (P<0.05). In the in vivo expts. using the PC-3 human **prostate** cancer mouse model, tumor volume and growth was lower in mice treated with Ad-CMV-TK/acyclovir than in those treated with Ad-CMV-TK only, acyclovir only or untreated (controls) (P<0.05). Histochem. staining of tumor tissues showed that Ad-CMV-TK/acyclovir destroyed PC-3 tumors through tumor cell death and apoptosis, with local lymphatic infiltration. The mean PCNA labeling index in **prostate** cancer cells of mice treated with Ad-CMV-TK/acyclovir was significantly lower than that in untreated controls (P<0.05, Mann-Whitney U-test). The Ki-67 labeling index in **prostate** cancer cells of mice treated with Ad-CMV-TK/acyclovir was also lower than that in untreated controls (P<0.05, Student's t-test). Adenovirus-mediated suicide-gene therapy using the HSV-TK gene decreased the proliferative activity of PC-3 human prostatic cancer cells in vivo. Conclusions: Adenovirus-mediated suicide-gene therapy using an HSV-TK/acyclovir system provided effective therapy in an exptl. human **prostate** cancer mouse model, by significantly inhibiting tumor growth and decreasing the proliferative activity of human **prostate** cancer cells. Such therapy could be developed as a novel method for treating patients with **androgen-independent prostate** cancer.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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                "PROSTATE GLAND, NEOPLASM"/CV) OR PROSTATE?
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L15       84636 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 OR ESTRADIOL
L16       18241 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15(L)(LOWER? OR REDUC?)
L22         579 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16 AND L9
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L35         168 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33 AND L31
L36          71 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L35 AND ANDROGEN(W)INDEPENDENT

L37           5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L36 AND PRODRUG
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L39          28 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L38 NOT L37


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L39  ANSWER 1 OF 28  HCAPLUS  COPYRIGHT 2005 ACS on STN
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ACCESSION NUMBER: 2005:211436 HCAPLUS
DOCUMENT NUMBER: 142:481284
TITLE: Diet, exercise and **prostate** cancer
AUTHOR(S): Barnard, R. James; Aronson, William J.
CORPORATE SOURCE: Department of Physiological Science and Department of Urology, University of California, Los Angeles, CA, 90095-1606, USA
SOURCE: Horizons in Cancer Research (2004), 1(Prostate Cancer), 1-21
CODEN: HCROAG
PUBLISHER: Nova Science Publishers, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. It has been suggested that a large part of the international variation in **prostate** cancer mortality might be explained by diet and exercise. Countries with a very low mortality generally consume a low-fat diet and are phys. active compared to countries with a high **prostate** cancer mortality. When men from countries with a high **prostate** cancer mortality are placed on a low-fat diet and/or exercise program serum levels of insulin, free testosterone, **estradiol** and IGF-1 are **reduced** while SHBG and IGFBP-1 are elevated. These in vivo serum changes directly impact on **androgen-dependent prostate** cancer cell lines in vitro to **reduce** cell growth and induce apoptosis. The **reduction** in serum IGF-1 and increase in IGFBP-1 with diet and exercise appear to be the most significant as they lead to an increase in tumor cell p53 protein and its down-stream effector p21 which are responsible for the **reduction** in cell growth and induced apoptosis. Preliminary results from a clin. study with men on "Watchful Waiting" indicate that the observed in vitro effects of diet and exercise on **prostate** cancer cell growth also occur in vivo.
REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 2 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:109775 HCAPLUS
DOCUMENT NUMBER: 143:462
TITLE: Effects of 5 alpha reductase inhibitors on **androgen-dependent** human prostatic carcinoma cells
AUTHOR(S): Festuccia, Claudio; Angelucci, Adriano; Gravina, Giovanni Luca; Muzi, Paola; Vicentini, Carlo; Bologna, Mauro
CORPORATE SOURCE: Prostate Biology Laboratory Department of Experimental Medicine, University of L'Aquila Science and Technology School, l'Aquila, 67100, Italy
SOURCE: Journal of Cancer Research and Clinical Oncology (2005), 131(4), 243-254
CODEN: JCROD7; ISSN: 0171-5216
PUBLISHER: Springer GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To investigate the effects of MK906, a selective 5 alpha reductase (5αR) type 2 (5αR2) inhibitor, and of MK386, a specific 5αR1 inhibitor, on the cellular proliferation of **androgen-dependent** human prostatic cancer (PCa) cells in cultures of cells derived from biotic and surgical tissues. In this study we tested the effects of MK906 and MK386 in 30 cultures derived from PCa, 6 from PIN and 10 from benign prostatic hyperplasia specimens. **Prostate** primary cultures under short-term conditions (with <4 subcultures)

represent a mixture of epithelial and stromal cells. Epithelial cells require testosterone (T) for optimal growth, but were not able to grow in the presence of T under long-term conditions even if DHT was able to induce cellular proliferation to a similar extent in both conditions, suggesting that 5αR can be lost in long-term cultures. Therefore, our studies were performed under short-term conditions. Both 5αR inhibitors decreased cell proliferation significantly and dose-dependently in all the samples tested. MK906 was more efficient than MK386 in 7 out of 10 cultures derived from BPH tissues, in 4 out of 6 cultures derived from PIN and in 18 out of 30 cultures derived from PCa. In 3 out of 10 BPH, in 2 out of 6 PIN and in 5 out of 30 PCa-derived cultures, both inhibitors presented similar efficacy, whereas in 1 out of 10 BPH and 7 out of 30 PCa-derived cultures MK386 was more efficient than MK906. In addition, MK386 was more efficient than MK906 in 4 out of 15 non-metastatic PCa and 2 out of 7 metastatic PCa-derived cultures. Considering that 5αR1 (responsible primarily for androgenic catabolism) is mostly expressed in epithelial cells and that 5αR2 (responsible for local DHT synthesis and release) is expressed in the stromal cells (which provides several paracrine growth factors and DHT itself to the epithelial cells), our expts. suggest that the inhibition of both 5αR1 and 5αR2 by MK386 and MK906, resp., may have therapeutic potential in order to reduce the growth and progression of human prostatic cancers, through the inhibition of autocrine or paracrine mechanisms involving the stromal cell compartment. In addition, some effects of 5αR inhibitors could be mediated by estrogens, which are synthesized by the aromatase enzyme present in the epithelial cells. These aspects could be considered in order to improve the therapeutical management of PCa and for future clin. trials.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 3 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:86100 HCAPLUS
DOCUMENT NUMBER: 143:57304
TITLE: Preclinical models relevant to diet, exercise, and cancer risk
AUTHOR(S): Barnard, R. James; Aronson, William J.
CORPORATE SOURCE: Departments of Physiological Science and Urology, University of California, Los Angeles, Los Angeles, CA, 90095-1606, USA
SOURCE: Recent Results in Cancer Research (2005), 166(Tumor Prevention and Genetics III), 47-61
CODEN: RRCRBU; ISSN: 0080-0015
PUBLISHER: Springer GmbH
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Metabolic syndrome was initially described as an aggregation of risk factors for the development of coronary artery disease with insulin resistance and compensatory hyperinsulinemia as the underlying factor. In an earlier review, we suggested that hyperinsulinemia may also lead to **prostate** cancer (PCa), the most common male cancer in industrialized nations. Furthermore, we suggested that diet and exercise, known to be important in the development of insulin resistance, may also be important in the development of PCa. When we placed men from the United States on a low-fat diet and/or exercise program, serum levels of insulin, free testosterone, **estradiol** and insulin-like growth factor (IGF)-1 were **reduced** while sex hormone-binding globulin (SHBG) and insulin-like growth factor binding protein (IGFBP)-1 were elevated. These in vivo serum changes directly impacted on **androgen-dependent prostate** cancer cell lines

in vitro to **reduce** cell growth and induce apoptosis. The **reduction** in serum IGF-1 and increase in IGFBP-1 with diet and exercise appear to be the most significant, as these changes lead to an increase in tumor cell p53 protein and its down-stream effector p21, which are responsible for the **reduction** in cell growth and induced apoptosis. Preliminary results from a clin. study with men on "watchful waiting" indicate that the observed in vitro effects of diet and exercise on **prostate** cancer cell growth also occur in vivo.

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 4 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:659638 HCAPLUS
DOCUMENT NUMBER: 137:363333
TITLE: Effects of PC-SPES on proliferation and expression of AR/PSA in androgen-responsive LNCaP cells are independent of estradiol
AUTHOR(S): Hsieh, Tze-Chen; Xiong, Wen; Traganos, Frank; Darzynkiewicz, Zbigniew; Wu, Joseph M.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, New York Medical College, Valhalla, NY, 10595, USA
SOURCE: Anticancer Research (2002), 22(4), 2051-2060
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Previous studies have suggested that the clin. efficacy of PC-SPES, a dietary supplement used frequently by men diagnosed with **androgen -dependent** (AD) or androgen-independent (AI) **prostate** cancer (CaP), is mechanistically attributed to estrogenic components present in the herbal mixture To test this hypothesis, the authors compared **estradiol** (1 nM), potentially an active principle in PC-SPES, with PC-SPES (using an amount equivalent to 1 nM **estradiol**) on cell proliferation, induction of apoptosis, and regulation of **prostate** specific genes, PSA and AR, in androgen-responsive LNCaP cells. Cells cultured in steroid proficient (FBS) or-deficient (CS-FBS) media to simulate hormonal status pre- and post-castration in vivo, were incubated with **estradiol** or PC-SPES. Proliferation was **reduced** in PC-SPES treated cells cultured in media supplemented with FBS or CS-FBS; in contrast, addition of **estradiol** had no effect on proliferation in FBS cultures, and elicited a 45% growth increase in CS-FBS-supplemented cultures. The differential proliferative response of LNCaP cells to PC-SPES vs. **estradiol** was also supported by changes in PCNA expression, cell viability, cell cycle phase distribution, and induction of apoptosis. **Estradiol** elicited time-dependent increases in secreted PSA, whereas PC-SPES suppressed PSA secretion, in both culture conditions. In FBS cultures, PC-SPES **lowered** intracellular AR and PSA by 61% and 17%, resp., while **estradiol** increased intracellular PSA, in parallel with a 42% decrease in AR expression. In comparison with cells maintained with CS-FBS, **estradiol** induced substantial increases in both intracellular PSA and AR, whereas PC-SPES resulted in a smaller increase in intracellular PSA without affecting the expression of AR. These studies show that the antiproliferative and gene modulatory effects of PC-SPES in **androgen-dependent** human **prostate** cancer cells are mechanistically and functionally distinct from effects attributable to **estradiol.**

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 5 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:560370 HCAPLUS
DOCUMENT NUMBER: 137:276231
TITLE: Estrogen sulfotransferase: Discrete and **androgen-dependent** expression in the male reproductive tract and demonstration of an in vivo function in the mouse epididymis
AUTHOR(S): Tong, M. H.; Song, W.-C.
CORPORATE SOURCE: Center for Experimental Therapeutics and Department of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104, USA
SOURCE: Endocrinology (2002), 143(8), 3144-3151
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Estrogen sulfotransferase (EST) catalyzes the sulfoconjugation and inactivation of the steroid hormone estrogen. It is known previously that EST is expressed abundantly in Leydig cells of the testis. We recently have shown that male mice with targeted EST gene disruption developed age related Leydig cell and seminiferous tubule abnormalities as a consequence of increased local estrogen stimulation. In the same study, we also found that epididymal sperm isolated from the mutant mice had significantly **reduced** motility, but whether this reflected impaired epididymal function or was secondary to the testicular lesions was not known. The purpose of the current study was to investigate if EST is normally present in the mouse epididymis and/or other parts of the male reproductive tract where, as in testis, it may play a role in regulating local estrogen homeostasis. We describe here that EST is expressed in the epithelium of corpus and cauda but not caput regions of the mouse epididymis. It is also expressed in the luminal epithelium and smooth muscle cells of the vas deferens but was present at very low levels, if at all, in the **prostate** or seminal vesicle/ coagulating gland. Hypophysectomy, castration, and epididymal ligation expts., together with the use of an androgen receptor antagonist, established that EST expression in the epididymis and vas deferens is critically dependent on pituitary hormone(s) and androgen but not on other factors in the testicular fluid. Administration of exogenous **estradiol** to mice with surgically ligated epididymis resulted in a more pronounced **reduction** in sperm motility in EST mutant mice than in wild-type mice. We conclude that EST is discretely expressed and regulated in the male reproductive tract and plays a physiol. role in maintaining the functional integrity of the epididymis by regulating luminal estrogen homeostasis.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 6 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:483868 HCAPLUS
DOCUMENT NUMBER: 137:167621
TITLE: Evaluation of the pituitary-testicular function during experimental nephrosis
AUTHOR(S): Menjivar, M.; Ortiz-Lopez, M. G.; Vilchis, F.; Diaz-Bonilla, L.; Zambrano, E.; Zarinan, T.; Pedraza-Chaverri, J.
CORPORATE SOURCE: Department of Biology, Faculty of Chemistry, Universidad Nacional Autonoma de Mexico, Mexico City, Mex.
SOURCE: Life Sciences (2002), 70(23), 2769-2782
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal
LANGUAGE: English
AB To investigate the pituitary-testicular function in nephrotic rats, a sequence of expts. was undertaken in adult male rats after a single dose of puromycin aminonucleoside (PAN). Endocrine modifications were evaluated chronol. throughout the exptl. disease in order to determine the appearance of hormone alterations which lead to the axis dysfunction. Serum concentration of LH, FSH, androstenedione, total and free testosterone, **estradiol** as well as urine testosterone were measured by specific RIAs on days 3, 7 and 10 after treatment on nephrotic and control groups. Prolactin was also evaluated on day 10. Likewise, total weight of various androgen responsive tissues from both groups was recorded, and the number of androgen receptor (AR) binding sites were determined To know the functional status of the hipophyseal-testicular unit, groups of nephrotic and control rats were stimulated with LHRH (300 ng/100 g b.w.) or with one or four doses of hCG (8 UI), resp. Addnl., the relative in vitro biol. activity of FSH from nephrotic and control rats before and after LHRH stimulus was determined The results from the hormonal profile revealed clear endocrine disorders characterized by a progressive diminution of all serum hormones except prolactin and urine testosterone, which remained unmodified. The weight of the main androgen responsive tissues, the ventral **prostate** and the seminal vesicle, decreased parallel to androgen diminution. The binding anal. of AR shows a significant elevation of the available androgen sites in all analyzed tissues except kidney and hypothalamus. The secretion of LH and FSH from nephrotic animals after LHRH administration was **lower** than that from intact animals at the registered times. Interestingly, the biol. activity of FSH from nephrotic rats was not detectable at both, before and after LHRH administration. Testicular response to hCG stimuli, in terms of testosterone synthesis was not significantly different in the two groups analyzed with respect to the intact animals. By contrast, no response was observed in terms of **estradiol** production at either one or four doses of hCG. On the whole, the results presented herein allow us to conclude that exptl. nephrosis has a harmful effect on the pituitary-testicular axis, and strongly suggests that the endocrine dysfunction is initiated at the hypophyseal level; even though a specific testicular damage is also present.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 7 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:469244 HCAPLUS
DOCUMENT NUMBER: 137:167247
TITLE: Expression of **prostate**-specific antigen is transcriptionally regulated by genistein in **prostate** cancer cells
AUTHOR(S): Davis, Joanne N.; Kucuk, Omer; Sarkar, Fazlul H.
CORPORATE SOURCE: Department of Urology, University of Michigan Medical Center, Ann Arbor, MI, USA
SOURCE: Molecular Carcinogenesis (2002), 34(2), 91-101
CODEN: MOCAE8; ISSN: 0899-1987
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Prostate** cancer is the second-leading cause of cancer-related deaths in men in the United States. Unfortunately, there is no effective therapy when **prostate** cancer becomes metastatic and refractory to conventional treatments. For this reason, the identification and exploration of new agents that **reduce prostate** cancer cell growth are of paramount importance. High consumption of

plant-derived phytoestrogens is inversely associated with the incidence and mortality rate of **prostate** cancer. Previous studies, including our own, have shown that the phytoestrogen genistein inhibits **prostate** cancer cell growth in vitro and in vivo and decreases secreted and intracellular levels of the androgen-regulated protein **prostate**-specific antigen (PSA), but the role of genistein as an agonist/antagonist for hormone receptors remains unclear. To elucidate the mechanism by which genistein modulates PSA protein expression in **prostate** cancer cells, we investigated the effects of genistein on androgen-mediated and estrogen-mediated transcriptional regulation of PSA, androgen receptor (AR) mRNA and protein expression, and the ability of nuclear proteins to bind to androgen-response elements (AREs) in LNCaP cells. We showed that genistein decreased the transcriptional activation of PSA by both **androgen-dependent** and androgen-independent methods in LNCaP cells. The **reduction** of androgen-mediated transcriptional activation of PSA was correlated with decreased AR protein and mRNA levels and decreased binding to AREs. In contrast, genistein had differential effects on 17β- **estradiol** -mediated PSA expressions. Low concns. of genistein enhanced 17β- **estradiol**-mediated PSA expressions, whereas high concns. of genistein inhibited estrogen-mediated PSA expression in LNCaP cells. Genistein did not inhibit AR protein expression in the presence of 17β- **estradiol.** These results suggest that ligand-dependent differences in the ability to activate PSA expression may contribute to the agonistic/antagonistic responses observed with genistein in **prostate** cancer cells.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 8 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:310175 HCAPLUS
DOCUMENT NUMBER: 136:380361
TITLE: Androgen administration in middle-aged and ageing men: Effects of oral testosterone undecanoate on dihydrotestosterone, estradiol and **prostate** volume
AUTHOR(S): Pechersky, A. V.; Mazurov, V. I.; Semiglazov, V. F.; Karpischenko, A. I.; Mikhailichenko, V. V.; Udintsev, A. V.
CORPORATE SOURCE: The Department of Urology and Andrology, Medical Academy of Post-Diploma Education, St Petersburg, 197373, Russia
SOURCE: International Journal of Andrology (2002), 25(2), 119-125
CODEN: IJANDP; ISSN: 0105-6263
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The gradual **reduction** of plasma testosterone in middle-aged and older men from mid-life onwards coincides paradoxically with the time when there is progressive growth of the **prostate**, a highly **androgen-dependent** organ. The growing interest in androgen therapy for older men makes it essential to understand the effects of exogenous testosterone on the non-diseased **prostate**, yet few studies are available. The present study examined **prostate** volume, **prostate**-specific antigen (PSA) and **lower** urinary tract symptom (IPSS) score in 207 men, aged 40-83 yr, presenting with clin. features of age-related androgen deficiency [sexual and/or urinary dysfunction, elevated LH (LH)] who were treated for 6 mo with oral testosterone undecanoate (TU). Men were divided into two groups, group 1

(n = 92, plasma testosterone levels > 13 nmol/L) were treated with 80 mg daily; group 2 (n = 115, plasma testosterone levels < 13 nmol/L) were treated with given 120 mg daily. Before treatment and after 1, 3 and 6 mo of treatment, **prostate** volume was measured by ultrasound and hormones [testosterone, dihydrotestosterone, **estradiol**, LH, FSH (FSH)] and PSA were measured. Within 1 mo of treatment, the elevated blood LH levels were markedly decreased in all men in group 1, as well as most men in group 2. Group 2 was subdivided into men whose LH levels were suppressed (n = 95, group 2a) and those whose LH levels did not suppress (n = 20, group 2b). Men in group 1 and 2a had marked decreases in **prostate** volume, PSA and **lower** urinary tract symptom (IPSS) scores whereas no significant changes were observed in group 2b. Groups 1 and 2a also had more striking suppression of LH, FSH, dihydrotestosterone and **estradiol** whereas group 2b had no significant increases in blood testosterone concns. These findings suggest that exogenous testosterone in middle-aged and older men with some clin. features of age-related androgen deficiency can retard or reverse **prostate** growth and that elevated plasma LH may be a useful index of severity of age-related androgen deficiency.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 9 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:121668 HCAPLUS
DOCUMENT NUMBER: 136:257469
TITLE: **Androgen-dependent** regulation of human MUC1 mucin expression
AUTHOR(S): Mitchell, Stephen; Abel, Paul; Madaan, Sanjeev; Jeffs, James; Chaudhary, Khurram; Stamp, Gordon; Lalani, El-Nasir
CORPORATE SOURCE: Department of Histopathology, Faculty of Medicine, Imperial College, London, W12 0NN, UK
SOURCE: Neoplasia (New York, NY, United States) (2002), 4(1), 9-18
CODEN: NEOPFL; ISSN: 1522-8002
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB MUC1 mucin is transcriptionally regulated by estrogen, progesterone, and glucocorticoids. The authors' objective was to determine whether androgen receptor (AR) activation regulates expression of MUC1. The following breast and prostatic cell lines were phenotyped and grouped according to AR and MUC1 protein expression: (1) AR+MUC1+ [DAR17+19 (AR transfectants of DU-145), ZR-75-1, MDA-MB-453, and T47D]; (2) AR-MUC1+ [DZeo1 (AR - vector control), DU-145, BT20, MDA-MB-231, and MCF7]; (3) AR+MUC1 - (LNCaP and LNCaP-r). Cell proliferation was determined using the MTT assay in the presence of synthetic androgen R1881, 0.1 pM to 1 μM. Cell surface MUC1 expression was determined by flow cytometry in the presence or absence of **estradiol**, medroxy progesterone acetate or R1881, with and without 4 hydroxy-flutamide (4-OH), a nonsteroidal AR antagonist. The functional significance of MUC1 expression was investigated with a cell-cell aggregation assay. Only AR+ MUC1+ cell lines showed a significant increase in MUC1 expression with AR activation, reversed in the presence of 4-OHF. Cell proliferation was unaffected. Increased expression of MUC1 was associated with a significant **reduction** in cell-cell adhesion. To the authors' knowledge, this is the first description of **androgen-dependent** regulation of MUC1 mucin. This is also functionally associated with decreased cell-cell adhesion, a recognized feature of progressive malignancy. These findings have important implications for physiol. and pathol. processes.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 10 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:585427 HCAPLUS
DOCUMENT NUMBER: 135:236697
TITLE: 2-Methoxyestradiol blocks cell-cycle progression at G2/M phase and inhibits growth of human **prostate** cancer cells
AUTHOR(S): Kumar, Addanki P.; Garcia, Gretchen E.; Slaga, Thomas J.
CORPORATE SOURCE: Center for Cancer Causation and Prevention, AMC Cancer Research Center and University of Colorado Comprehensive Cancer Center, Denver, CO, 80214, USA
SOURCE: Molecular Carcinogenesis (2001), 31(3), 111-124
CODEN: MOCAE8; ISSN: 0899-1987
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 2-Methoxyestradiol (2-ME), an endogenous metabolite of 17β-**estradiol**, is present in human blood and urine. Here the authors show for the first time that 2-ME significantly inhibited the growth of normal **prostate** epithelial cells and **androgen-dependent** LNCaP and androgen-independent DU145 **prostate** cancer cells. This growth inhibition was accompanied by a twofold increase in the G2/M population, with a concomitant decrease in the G1 population, as shown by cell-cycle anal. 2-ME treatment affected the cell-cycle progression of **prostate** cancer cells specifically by blocking cells in the G2 phase. Immunoblot anal. of the key cell-cycle regulatory proteins in the G2/M phase showed a 14-fold increase in the expression of p21 and an eightfold increase in the expression of p34 cell division cycle 2 (cdc2). The authors also found an accumulation of phosphorylated cdc2 after 2-ME treatment. Furthermore, Wee 1 kinase was detectable after 2-ME treatment. 2-ME treatment also led to an increase in the activity of caspase-3, followed by apoptosis, as shown by terminal deoxynucleotidyltransferase-mediated deoxyuridine 5-triphosphate-biotin nick end-labeling and fluorescein isothiocyanate-poly(ADP-ribose) polymerase assay. Estrogen receptor levels did not change after treatment with 2-ME. Examination of the signaling pathways that mediate 2-ME-induced apoptosis showed **reduction** in the level of p53 expression and its DNA-binding activity. Given the fact that p53 mutations are common in patients with metastatic **prostate** cancer, the authors' finding that 2-ME-mediated growth inhibition of human **prostate** cancer cells occurred in a p53-independent manner has considerable clin. significance. These findings, combined with the limited toxicity of 2-ME, may have significant implications for alternative treatment of advanced **prostate** cancer.
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 11 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:110766 HCAPLUS
DOCUMENT NUMBER: 133:41649
TITLE: Androgen receptor gene polymorphism and **prostate** zonal volumes in Australian and Chinese men
AUTHOR(S): Jin, B.; Beilin, J.; Zajac, J.; Handelsman, D. J.
CORPORATE SOURCE: Andrology Unit, Royal Prince Alfred Hospital & Department of Medicine, University of Sydney, Australia

SOURCE: Journal of Andrology (2000), 21(1), 91-98
CODEN: JOAND3; ISSN: 0196-3635
PUBLISHER: American Society of Andrology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Prostate** diseases are age and **androgen dependent.** The evolution of clin. overt pathol. requires decades of exposure to adult male levels of circulating testosterone, but the precise relationship between age and androgen circulation remains poorly understood. A marker of integrated androgen action over prolonged periods would therefore be a valuable tool for clin. and epidemiol. research into the origins of **prostate** disease. To evaluate these 2 factors, the authors have studied the CAG-repeat length polymorphism of the androgen receptor gene and the size of the total, central, and peripheral zones of the **prostate**, estimated by planimetric ultrasound in 2 populations with widely different susceptibility to death from invasive **prostate** cancer. From a larger epidemiol. study of the effects of ethnicity and migration on the origins of **prostate** disease, a nested-case control study was undertaken with 50 Chinese men living in Yue Yang, China and 50 non-Chinese men living in Sydney, Australia. All men had undergone planimetric transrectal **prostate** ultrasound together with blood sampling to determine CAG-repeat length by PCR and immunoassay of plasma testosterone, **estradiol**, dihydrotestosterone (DHT), sex hormone-binding globulin (SHBG), and **prostate**-specific antigen (PSA). Australian men had larger central (7.9 ± 0.4 vs 3.3 ± 0.3 mL) and total (29.8 ± 1.2 vs 25.5 ± 1.1 mL) but not peripheral (22.0 ± 0.9 vs 22.2 ± 0.8 mL) **prostate** vols. compared with Chinese men. Even after adjustment for differences in body size (the Australian men were taller and heavier), the central-zone volume remained **lower** by 50% in Chinese men ($P < 0.001$), whereas testis and total-**prostate** vols. were no longer significantly different. The length of CAG repeats was no different between Australian men (22.5 ± 0.5 repeats) and Chinese men (22.5 ± 0.5 repeats), and there was no correlation within or between populations in CAG repeats or any measure of **prostate** volume or hormones. DHT concentration was 20% **lower** in Chinese men compared with Australian men (1.6 ± 0.1 vs 2.0 ± 0.1 nmol/L, $P = 0.005$), a difference that persisted after age adjustment ($P = 0.039$) but that was removed by adjustment for differences in total-**prostate** size ($P = 0.12$). Blood testosterone, **estradiol**, SHBG, and PSA concns. were not different between the 2 populations. Hence, the hypothesis is refuted that the CAG repeat polymorphism in the androgen receptor gene (within the nonpathol. range) and the central-**prostate** zone volume might be markers of long-term androgen sensitivity. Whether either factor alone may constitute a marker of androgen sensitivity remains to be established by other means, and a long-term marker of integrated androgen action suitable for clin. and epidemiol. research is still lacking.

REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 12 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:699006 HCAPLUS
DOCUMENT NUMBER: 130:64746

TITLE: Age-dependent and lobe-specific spontaneous hyperplasia in the brown Norway rat **prostate**

AUTHOR(S): Banerjee, Partha P.; Banerjee, Subhadra; Lai, James M.; Strandberg, John D.; Zirkin, Barry R.; Brown, Terry R.
CORPORATE SOURCE: Division of Reproductive Biology, Johns Hopkins School of Medicine, Baltimore, MD, 21205, USA

SOURCE: Biology of Reproduction (1998), 59(5), 1163-1170
CODEN: BIREBV; ISSN: 0006-3363
PUBLISHER: Society for the Study of Reproduction
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors showed previously that exogenously administered testosterone caused age- and lobe-specific overgrowth of the **prostate** in Brown Norway rats. A common feature observed in testosterone-treated animals was cell hypertrophy in each of the ventral, dorsal, and lateral lobes of both young (6 mo old) and old (24 mo old) rats. By contrast, hyperplasia was seen only in the dorsal and lateral lobes of old rats treated with testosterone. These observations prompted the authors to examine whether age- and lobe-specific overgrowth might also occur in untreated rats as a consequence of the endogenous hormonal milieu. To this end, blood and **prostates** were collected from a large number (25-30 rats per group) of 4- to 6-mo-old (young) and 21- to 24-mo-old Brown Norway rats. Both serum testosterone (-45%) and **estradiol** (-22%) concns. decreased significantly with age, but the greater magnitude of the decrement in testosterone relative to **estradiol** led to a **reduction** in the serum testosterone:**estradiol** ratio. Paradoxically, although the **prostate** is **androgen dependent**, the wet weight, protein, and DNA contents increased significantly with age in the dorsal and lateral lobes of old rats despite the decrease in testosterone level. Histol. examination revealed that the increased wts. and DNA contents of the dorsal and lateral lobes in old rats coincided with an increased number of epithelial cells in the distal and intermediate segments of these lobes, indicative of hyperplasia but independent of change in cell size. Taken together, these results show a spontaneous age-related overgrowth of cells in the dorsal and lateral prostatic lobes of old Brown Norway rats despite diminished serum testosterone concns. The aging Brown Norway rat, therefore, may be a useful model for studies of some aspects of the pathogenesis underlying spontaneous age-related prostatic hyperplasia.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 13 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:601738 HCAPLUS
DOCUMENT NUMBER: 129:298517
TITLE: Sensitivity of a Tier I screening battery compared to an in utero exposure for detecting the estrogen receptor agonist 17β-estradiol
AUTHOR(S): O'Connor, John C.; Frame, Steven R.; Biegel, Lisa B.; Cook, Jon C.; Davis, Leonard G.
CORPORATE SOURCE: DuPont Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE, 19714, USA
SOURCE: Toxicological Sciences (1998), 44(2), 169-184
CODEN: TOSCF2; ISSN: 1096-6080
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A Tier I screening battery for detecting endocrine active compds. (EACs) has been evaluated for its ability to identify 17β- **estradiol** , a pure estrogen receptor agonist. In addition, the responses obtained with the Tier I battery were compared to the responses obtained from F1 generation rats from a 90-day/one-generation reproduction study with 17β-**estradiol** to characterize the sensitivity of the Tier I battery against the sensitivity of an in utero exposure for detecting EACs. The Tier I battery incorporates two short-term in vivo tests (5-day ovariectomized female battery; 15-day intact male battery) and an in vitro yeast transactivation system (YTS) for identifying compds. that alter

endocrine homeostasis. The Tier I female battery consists of traditional uterotrophic endpoints coupled with biochem. and hormonal endpoints. It is designed to identify compds. that are estrogenic/antiestrogenic or modulate dopamine levels. The Tier I male battery consists of organ wts. coupled with microscopic evaluations and a comprehensive hormonal assessment. It is designed to identify compds. that have the potential to act as agonists or antagonists to the estrogen, androgen, progesterone, or dopamine receptor; steroid biosynthesis inhibitors (aromatase, 5α-**reductase**, and testosterone biosynthesis); or compds. that alter thyroid function. The YTS is designed to identify compds. that bind to steroid hormone receptors (estrogen, androgen, and progesterone) and activate gene transcription. The profile generated for 17β-**estradiol** was characteristic of the responses expected with a pure estrogen receptor agonist. In the female battery, responses to 17β-**estradiol** included increases in uterine fluid imbibition, uterine weight, estrus conversion, uterine stromal cell proliferation, uterine epithelial cell height, uterine progesterone receptor content, serum prolactin and **estradiol** levels, and decreases in uterine estrogen receptor content and FSH and LH levels. In the male battery, responses to 17β- **estradiol** included decreases in absolute testis and epididymides wts., decreases in relative wts. for **androgen-dependent** tissues (**prostate**, seminal vesicles, and accessory sex gland unit), hormonal alterations (decreased serum testosterone, dihydrotestosterone, and LH and increased serum prolactin levels), and microscopic alterations of the testis and epididymides. In the YTS for the estrogen receptor, 17β-**estradiol** had an EC50 value of 7.2 + 10-9 M, while DHT and progesterone had little cross-activation. The androgen and progesterone receptor systems were less selective in that 17β- **estradiol** activated these systems within 3 orders of magnitude of the primary ligand. In the 90-day/one-generation reproduction study, responses to dietary administration of 17β- **estradiol** included alterations in organ wts., developmental landmarks, and hormonal levels. Comparison of the responses obtained with the authors' Tier I battery and an in utero exposure demonstrates that the Tier I screening battery is as sensitive as an in utero exposure for detecting 17β- **estradiol**-induced alterations in hormonal homeostasis. (c) 1998 Society of Toxicology.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 14 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:645749 HCAPLUS
DOCUMENT NUMBER: 123:74820
TITLE: Anti-androgen effects of the aromatase inhibitor, atamestane
AUTHOR(S): Shao, Tsang C.; Marcellj, Marco; Kong, Ann; Cunningham, Glenn R.
CORPORATE SOURCE: Department Medicine and Cell Biology, Baylor College of Medicine, Houston, TX, USA
SOURCE: Journal of Andrology (1995), 16(2), 100-7
CODEN: JOAND3; ISSN: 0196-3635
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Prostatic hyperplasia can be induced in both intact and castrated dogs and in intact cynomolgus monkeys by the administration of androgenic steroids. Estrogenic steroids potentiate this effect in dogs. These changes also can be induced by androstenedione, which increases androgen and estrogen levels. Atamestane (ATA; 1-methyl-3,17-dione-androsta-1,4-diene), a potent aromatase inhibitor, inhibits some of the androstenedione-induced effects; however, the nonsteroidal aromatase inhibitor, CGS-16949A, has

been reported to decrease serum **estradiol** levels in adult rats but to have no effect on **androgen-dependent** organ wts. To examine the mechanisms by which ATA affects the rat **prostate**, in vivo and in vitro studies were conducted using adult rat ventral **prostate** (VP). Intact Sprague-Dawley rats were injected daily for 14 days with sesame seed oil, ATA (70 mg/kg/day), finasteride (FIN; 5 mg/kg/day), a 5α- **reductase** inhibitor, or the combination of FIN plus ATA. A fifth group was castrated (CASTR) on day 1. The mean ± standard error VP weight of the controls was 350 ± 19 mg. It was **reduced** 17% ($P < 0.05$) by ATA, 29% ($P < 0.001$) by FIN, 48% ($P < 0.001$) by FIN plus ATA, and 86% ($P < 0.001$) by CASTR. The DNA/VP was **reduced** 22% (not significant) by ATA, 18% by FIN (not significant), 35% ($P < 0.01$) by FIN plus ATA, and 60% ($P < 0.001$) by CASTR. More significant changes were observed in RNA and protein. The mRNA for **prostatein** C3 was **reduced** by each of the treatments, but only CASTR increased the mRNA for TRPM-2, a marker of apoptosis. In VP explant cultures the effect of DHT on maintaining **prostatein** C3 mRNA was inhibited by ATA, and ATA was observed to compete with tritiated dihydrotestosterone ([3H]DHT) for binding to the cytosolic androgen receptor (AR) of the rat VP with an approx. ki of 3.5 + 10-4 M. To further investigate the anti-androgenic properties of ATA, CV-1 cells were transfected with expression plasmids encoding the human AR, cytomegalovirus-β-galactosidase, and the reporter plasmid, MMTV-CAT. DHT-activated expression of chloramphenicol acetyl transferase activity was **reduced** from 100% to 57% by 1 μM ATA and to 31% by 10 μM ATA. We conclude that ATA causes involution of the rat VP and that this effect is potentiated by the addition of FIN. It is likely that at least part of the effects of ATA on the rat VP are caused by anti-androgenic properties of ATA.

L39 ANSWER 15 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:481247 HCAPLUS
DOCUMENT NUMBER: 122:273872
TITLE: Evaluation of a novel redox-based estrogen chemical delivery system for the brain
AUTHOR(S): Rahimy, Mohamad H.; Bodor, Nicholas; Simpkins, James W.
CORPORATE SOURCE: College Pharmacy, University Florida, Gainesville, FL, 32610, USA
SOURCE: Trends Med. Chem. '90, Proc. Int. Symp. Med. Chem., 11th (1992), 369-76. Editor(s): Sarel, Shalom; Mechoulam, Raphael; Agranat, Israel. Blackwell: Oxford, UK.
CODEN: 60TTAQ
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Enhanced delivery and sustained release of **estradiol** (E2) in the brain are desirable for fertility regulation and for effective treatments of menopausal hot flushes and prostatic adenocarcinoma. Thus, we conducted studies to describe the pharmacokinetics and pharmacodynamics of a brain-enhanced E2-chemical delivery system (E2-CDS) in the rat. After systemic administration, the E2-CDS was rapidly oxidized to an intermediate quaternary ion (E2-Q+) with a t1/2 of about 29 min. However, the two major metabolites of E2-CDS, E2-Q+ and E2, exhibited a t1/2 in brain tissue of 8 days, while these were rapidly cleared from plasma and peripheral tissues. The long half-life of brain E2 is consistent with the observed pharmacodynamic responses to the E2-CDS. A single dose of E2-CDS suppressed plasma gonadotropins and testosterone (T) for 3 to 4 wk while other estrogens were only transiently effective. An E2-CDS dose-dependent **reduction** in serum T levels was observed by up to 97% at 7 days following

treatment and these low T levels were maintained with repeated dosing of E2-CDS. Consequently, the wts. of in situ **androgen-dependent** tissues (i.e. **prostate**) were **reduced** chronically, and the rate of growth of a prostatic adenocarcinoma was significantly **reduced.** Collectively, these studies indicate that E2-Q+ is preferentially "locked" into the brain and slowly hydrolyzes releasing E2. This sustained release of E2 locally in the brain chronically modifies brain E2-dependent processes.

L39 ANSWER 16 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:486578 HCAPLUS
DOCUMENT NUMBER: 119:86578
TITLE: Effects of neonatal estrogen exposure on prostatic secretory genes and their correlation with androgen receptor expression in the separate **prostate** lobes of the adult rat
AUTHOR(S): Prins, Gail S.; Woodham, Carl; Lepinske, Mark; Birch, Lynn
CORPORATE SOURCE: Coll. Med., Univ. Illinois, Chicago, IL, 60616, USA
SOURCE: Endocrinology (1993), 132(6), 2387-98
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The expression of lobe-specific, **androgen-dependent**, or androgen-responsive secretory genes was examined in **prostates** of rats given neonatal **estradiol** benzoate and this was directly compared with epithelial cell androgen receptor (AR) by using histol. techniques. Sprague-Dawley rat pups were given 25 μg **estradiol** benzoate or oil on days 1, 3, and 5 and killed on day 90. Prostatic mRNA was analyzed using Northern blots and in situ hybridization. Ventral lobe mRNA was hybridized with a **prostate** binding protein (PBP) cDNA probe, while lateral and dorsal mRNA were hybridized with RWB (seminal vesicle secretory protein or SVS-II), probasin, and DP1 cDNA probes. Sections adjacent to those used for in situ hybridization were stained for AR by immunocytochem. Neonatal **estradiol** benzoate **reduced** ventral lobe PBP message on Northern blots, and this was not restored with adult testosterone administration. There was a direct correlation between epithelial cell AR and PBP expression, in that PBP message and protein were only present in epithelial AR-pos. cells and were absent in all AR-neg. epithelium. In the lateral **prostate**, probasin expression was unaffected by neonatal **estradiol** benzoate, whereas RWB was slightly **reduced** as detected by Northern anal. By in situ hybridization, these messages were observed at normal levels in lateral lobe epithelial cells of estrogenized rats, which directly correlated with the presence of AR in those cells. In the dorsal **prostate**, different response patterns to neonatal **estradiol** benzoate were found for the three secretory genes analyzed. On Northern blots, DP1 message declined, probasin mRNA was modestly suppressed, and RWB expression was elevated compared to those in control tissue. In situ hybridization revealed that RWB expression in estrogenized dorsal lobes was amplified in AR-pos. epithelial cells, whereas AR-neg. cells appeared unaltered. Thus, prostatic functional activity after neonatal **estradiol** benzoate exposure is affected in a lobe-specific manner, which correlates with the AR imprints in the sep. lobes.

L39 ANSWER 17 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:518329 HCAPLUS
DOCUMENT NUMBER: 117:118329
TITLE: Prolonged suppression of androgens and

androgen-dependent tissues by a brain-enhanced estrogen delivery system in the rat

AUTHOR(S): Rahimy, Mohamad H.; Bodor, Nicholas; Simpkins, James W.

CORPORATE SOURCE: Coll. Pharm., Univ. Florida, Gainesville, FL, 32610, USA

SOURCE: Journal of Biopharmaceutical Sciences (1991), 2(1), 25-43
CODEN: JBISE2; ISSN: 0957-7548

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The primary objective of hormone therapy in **prostate** cancer patients is to induce an effective androgen suppression, thus abolishing the growth promoting effects of androgens on the diseased **prostate** . High-dose estrogen therapy is as effective as castration (CAST) in this regard. An estrogen-chemical delivery system (E2-CDS), with sustained release of **estradiol** (E2) in the brain, may be potentially advantageous in the treatment of prostatic cancer by virtue of the need for **lower** or less frequent doses of estrogen. Thus, the effects of E2-CDS vs. CAST on androgen levels and wts. of androgen-responsive tissues were investigated in male rats. A single dose of E2-CDS (0.5 mg/kg) was as effective as CAST in suppressing the plasma testosterone (T) levels by 96% or 76% at 7 or 14 days after treatment, resp. The single injection of E2-CDS significantly **reduced** the wts. of **prostate** by 56% and seminal vesicles by 45% while CAST **reduced** the wts. of these tissues by 67% (**prostate**) or 52% (seminal vesicles) at 7 days post-treatment. **Prostate** and seminal vesicle wts. remained significantly suppressed through 14 days after CAST or E2-CDS treatment. Multiple injections of E2-CDS, given once a week for 2 or 3 consecutive weeks, resulted in significant **redn** . of the **prostate** as well as seminal vesicle wts. equivalent in magnitude and duration to the effect of CAST at 7 days after the last injection (2 and 3 injections paradigm) or at 14 days after the last injection (3 injections paradigm). Interestingly, both the suppression of T levels and the prolonged regression of tissue wts. caused by E2-CDS treatment were observed even in the face of low plasma E2 levels. E2-CDS had no significant effect on testis wts.; however, anterior pituitary wts. were increased by E2-CDS treatment in a manner related to the number of injections and the time since last dosing. CAST resulted in significant elevation of plasma gonadotropin levels, while E2-CDS treatment did not affect the plasma levels of these hormones. In conclusion, these data support the concept that the E2-CDS may be useful in the treatment of **androgen-dependent** prostatic hyperplasia.

L39 ANSWER 18 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1991:542132 HCAPLUS

DOCUMENT NUMBER: 115:142132

TITLE: The effects of a brain-enhanced estradiol delivery system on testosterone and **androgen-dependent** tissues. II. The role of testosterone

AUTHOR(S): Anderson, Wesley R.; Rahimy, Mohamad H.; Brewster, Marcus E.; Bodor, Nicolas; Simpkins, James W.

CORPORATE SOURCE: Coll. Pharm., Univ. Florida, Gainesville, FL, 32610, USA

SOURCE: Endocrinology (1991), 129(2), 726-33
CODEN: ENDOAO; ISSN: 0013-7227

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The present study was undertaken to evaluate the efficacy of an

estradiol-chemical delivery system (E2-CDS) for the brain vs. **estradiol** benzoate (E2-BNZ) in suppressing serum testosterone (T) and wts. of the ventral **prostate** and seminal vesicle in male rats. Also, the role of serum T in the weight **reduction** of **androgen-dependent** tissues observed after E2-CDS treatment was further evaluated in these studies. A single injection of E2-CDS suppressed serum T levels by 96%, 83%, 46%, or 63% 1, 7, 14, or 21 days after treatment, resp. In contrast, an equimolar dose of E2-BNZ had no significant effect on serum T at any sampling time examined **Prostate** weight was maximally **reduced** by 53% at 7 days and remained significantly suppressed by more than 31% throughout the 21-day time course. Similarly, seminal vesicle weight was **reduced** by 14% on day 1, maximally **reduced** by 41% on day 7 and remained significantly suppressed through day 21. In contrast, E2-BNZ was ineffective in inducing weight changes in either of these tissues. Serum PRL was significantly elevated through day 14, while E2 was elevated through day 7 by E2-CDS. Both the anterior pituitary and adrenal gland wts. were stimulated by E2-CDS treatment. Testis weight was moderately **reduced** by both esters. In a subsequent study serum T was **reduced** by 98% and 97% 1 and 7 days, resp., after E2-CDS treatment, and wts. of the ventral **prostate** and seminal vesicle were **reduced** by 47% and 40%, resp., at 7 days. In contrast, in rats treated with Silastic capsules containing T, the expected E2-CDS-induced weight regression was prevented in both **prostate** and seminal vesicles. These data indicate that the prolonged effects of E2-CDS on wts. of **androgen-dependent** tissues are caused by its ability to produce profound suppression of the serum T concentration

L39 ANSWER 19 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:542131 HCAPLUS
DOCUMENT NUMBER: 115:142131
TITLE: The effects of a brain-enhanced estradiol delivery system on testosterone and **androgen-dependent** tissues. I. Dose-response and time-course evaluation
AUTHOR(S): Rahimy, Mohamad H.; Anderson, Wesley R.; Brewster, Marcus E.; Bodor, Nicolas; Simpkins, James W.
CORPORATE SOURCE: Coll. Pharm., Univ. Florida, Gainesville, FL, 32610, USA
SOURCE: Endocrinology (1991), 129(2), 717-25
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The primary objective underlying hormone treatment of prostatic adenocarcinoma is to induce an effective androgen deprivation, and high dose estrogen therapy is as effective as surgical castration in abolishing the growth-promoting effects of androgens on prostatic tissue. An **estradiol**-chemical delivery system (E2-CDS), with sustained release of E2 in the brain, may be potentially useful in the treatment of prostatic cancer by virtue of the need for **lower** or less frequent doses of the estrogen. In this study the dose- and time-dependent effects of the E2-CDS vs. 17β-E2 on serum testosterone (T) and wts. of **androgen-dependent** tissues in male rats was evaluated. Rats received a single i.v. injection of E2-CDS (0.1, 0.5, or 1.0 mg/kg), equimolar doses of 17β-E2, or the drug's vehicle. The E2-CDS exhibited a dose- and time-dependent suppression of serum T and wts. of the ventral **prostate** and seminal vesicles. In contrast, 17β-E2 had no significant effect on serum T or growth of these **androgen-dependent** tissues. Serum T levels were significantly **reduced** by 98%, 82%, and 59% at 1, 7, and 14 days,

resp., with the 1.0 mg/kg dose of E2-CDS. The E2-CDS significantly **reduced prostate** weight by 45% and 50% (1.0- and 0.5-mg/kg doses, resp.) 7 days and by 27% (0.5 mg/kg dose) 14 days after treatment. Similarly, seminal vesicle wts. were **reduced** by 14-20% on day 1, maximally **reduced** by 39-48% on day 7, and still **reduced** by 24-36% on day 14 compared with the control levels. Wts. of these tissues returned to control levels by day 21. Serum E2 was elevated through 7 days by E2-CDS or on day 1 only by 17β-E2. PRL secretion was stimulated for 1 wk by both forms of estrogen. Anterior pituitary wts. were increased by the E2-CDS through 14 days, while 17β-E2 had no significant effect. These data indicate that the E2-CDS causes chronic suppression of serum T, which subsequently results in regression of **androgen-dependent** tissue weight

L39 ANSWER 20 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:442172 HCAPLUS
DOCUMENT NUMBER: 115:42172
TITLE: Effects of androgen and antiandrogen treatment on canine prostatic arginine esterase
AUTHOR(S): Juniewicz, Paul E.; Barbolt, T. A.; Egy, M. A.; Frenette, G.; Dube, J. Y.; Tremblay, R. R.
CORPORATE SOURCE: Dep. Oncopharmacol., Sterling Res. Group, Rensselaer, NY, 12144, USA
SOURCE: Prostate (New York, NY, United States) (1990), 17(2), 101-11
CODEN: PRSTDS; ISSN: 0270-4137
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The regulation of the primary secretory protein of the canine **prostate** arginine esterase, by androgens and(or) new antiandrogens under development was investigated. In the 1st experiment, castration decreased prostatic arginine esterase levels relative to intact controls (0.26 and 17.0 μmol/min/mg protein, resp.). Treatment of castrate dogs with either 5, 10, or 20 silastic capsules (8 cm length) containing the androgen 5α-androstane-3α,17β-diol (3α-diol) plus 1 capsule containing **estradiol** (E2) or the i.m. injection of 25 mg 3α-diol and 0.25 mg E2 for 12 wk resulted in a dose-dependent increase in prostatic arginine esterase activity (6.8, 19.0, 21.3, and 14.2 μmol/min/mg protein, resp.). In the 2nd experiment, steroid treatment (10 3α-diol plus 1 E2 silastic capsules) of castrate dogs for 12 wk resulted in prostatic arginine esterase activity of 17.8 μmol/min/mg. Co-administration of the steroidal androgen receptor antagonist Win 49,596 (WIN) at doses of 0.625, 2.5, 10, or 40 mg/kg/day p.o., dose-dependently inhibited prostatic arginine esterase activity (14.9, 14.3, 3.4, and 0.21 μmol/min/mg, resp.) to levels similar to that observed in castrate controls (0.14 μmol/min/mg). Administration of the nonsteroidal androgen receptor antagonist flutamide at 10 mg/kg/day p.o. to steroid-induced dogs also inhibited arginine esterase activity (0.07 μmol/min/mg). In the last experiment, treatment of intact dogs with WIN at 0.625, 2.5, 10, and 40 mg/kg/day for 16 wk dose-dependently **reduced** arginine esterase levels (17.0, 16.3, 10.2, and 3.9 μmol/min/mg, resp.) compared to intact controls (14.4 μmol/min/mg). Histomorphol. and ultrastructural evaluation of **prostates** from dogs indicated that antiandrogen treatment resulted in glandular epithelial atrophy as well as a **reduction** in the number of secretory granules. The results of these expts. support that canine prostatic arginine esterase activity is under androgenic control, can be inhibited by antiandrogen treatment and may serve as a functional marker of the androgenic state of the **prostate.** Whether the effects of androgen and antiandrogens on prostatic arginine esterase is direct or

indirect due to a general inhibitory effect on secretory epithelial cell function requires addnl. study. Furthermore, subject to further evaluation, the steroidal androgen receptor antagonist, Win 49,596, may be useful in the treatment of **androgen-dependent** disorders of the **prostate.**

L39 ANSWER 21 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:136237 HCAPLUS
DOCUMENT NUMBER: 114:136237
TITLE: Medroxyprogesterone acetate and the nuclear uptake of testosterone and its metabolites by brain, pituitary gland and genital tract in male cynomolgus monkeys
AUTHOR(S): Michael, Richard P.; Bonsall, Robert W.; Zumpe, Doris
CORPORATE SOURCE: Sch. Med., Emory Univ., Atlanta, GA, 30322, USA
SOURCE: Journal of Steroid Biochemistry and Molecular Biology (1991), 38(1), 49-57
CODEN: JSBBEZ; ISSN: 0960-0760
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The synthetic progestin, medroxyprogesterone acetate (MPA), is used to treat male sex offenders, and it is also suppresses sexual activity in male monkeys. To examine the possibility that MPA may act as an anti-androgen in the primate brain, intact male cynomolgus monkeys were given MPA (40 mg i.m.) once a week for 16 wk, while control males received i.m. injections of vehicle. All males were then castrated and 3 days later were given 3 mCi [3H]testosterone ([3H]T) i.v.; 1 h after injection males were killed, and radioactivity in nuclear pellets obtained from the hypothalamus (HYP), preoptic area (POA), amygdala (AMG), septum, pituitary gland and genital tract was analyzed by HPLC. Concns. of [3H]T and [3H]dihydrotestosterone in nuclear pellets were 65-96% **lower** in MPA-treated males than in controls, but the aromatized metabolite, [3H] **estradiol**, which was the major form of radioactivity present in nuclear pellets from HYP, POA and AMG, was unchanged. There were no differences in concns. of [3H]T in supernatants from the tissues of MPA-treated and control males. Because the **reduced** nuclear uptake of androgen in brain occurred in males whose **androgen-dependent** behavior had been suppressed by MPA treatments, it is proposed that MPA may have anti-androgenic effects at the level of the cell nucleus in brain regions that control behavior.

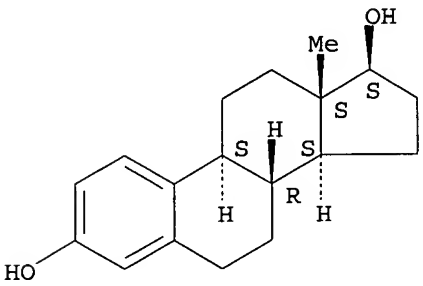
L39 ANSWER 22 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:172517 HCAPLUS
DOCUMENT NUMBER: 112:172517
TITLE: The influence of steroidal and nonsteroidal estrogens on the 5α-reduction of testosterone by the ventral **prostate** of the rat
AUTHOR(S): Makela, S.; Santti, R.; Martikainen, P.; Nienstedt, W.; Paranko, J.
CORPORATE SOURCE: Dep. Anat., Univ. Turku, Turku, SF-20520, Finland
SOURCE: Journal of Steroid Biochemistry (1990), 35(2), 249-56
CODEN: JSTBBK; ISSN: 0022-4731
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The 5α- **reduction** of testosterone to dihydrotestosterone (DHT) correlates with the androgen-mediated growth of the **prostate** under different exptl. and clin. conditions. The regulation of the prostatic growth and enzyme activity by steroidal and nonsteroidal estrogens was studied in rats. Estrogens did not activate the **androgen-dependent** 5α- **reductase** activity in cultured **prostate** of the rat. The direct inhibition of the

enzyme activity by estrogens at the concns. achievable in the male is not probable either. However, early estrogenization of the male rats in utero (on Day 17 of pregnancy) with diethylstilbesterol (DES) resulted in a persistent decrease of the enzyme activity and growth of the **prostate**, indicating a critical estrogen-sensitive period in the regulation of the ultimate enzyme activity. A similar DES-like inhibitory effect on the growth of the **prostate** was achieved by keeping animals from fertilization throughout the pregnancy until weaning on diet containing soy, rich in environmental estrogens. Zearalenone (Zeranol) and coumestrol, two nonsteroidal estrogens found in human and animal food, mimicked **estradiol** action in culture, but they were not estrogenic or antiestrogenic when administered to normal adults.

IT **50-28-2**, **Estradiol**, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(testosterone **reduction** by ventral **prostate** response to)

RN 50-28-2 HCAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol (17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



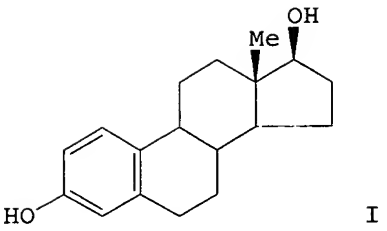
L39 ANSWER 23 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:400909 HCAPLUS
DOCUMENT NUMBER: 105:909
TITLE: Characterization of the **androgen-dependent** 22Kdalton glycoprotein from rat ventral **prostate**
AUTHOR(S): Wang, Tung Y.; Chamberlin, Linda L.; Xu, You H.
CORPORATE SOURCE: Dep. Biol. Sci., State Univ. New York, Buffalo, NY, 14260, USA
SOURCE: Journal of Steroid Biochemistry (1986), 24(4), 929-32
CODEN: JSTBBK; ISSN: 0022-4731
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Oxidation by mol. O converted the 22-kilodalton (Kdalton) glycoprotein from rat ventral **prostate** into a 34-kilodalton species, and this reaction could be reversed by thiol **reducing** reagent. Measurement of the level of the 22-Kdalton glycoprotein in prostatic cytosol by the radial immunodiffusion technique showed that changes in the 22-Kdalton glycoprotein concentration in response to androgen withdrawal and replacement were slow in comparison with androgen-regulated levels of mRNA coding for the protein. Charcoal absorption steroid-binding assays of the 22-Kdalton glycoprotein revealed that the protein did not bind testosterone [58-22-0], **estradiol**, progesterone, or corticosterone. Thus, 22-Kdalton glycoprotein is metabolically stable, not steroid-binding, and exists as an oligomer through disulfide

crosslinking.

L39 ANSWER 24 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1982:468118 HCAPLUS
DOCUMENT NUMBER: 97:68118
TITLE: Study of a proline-rich polypeptide bound to the prostatic binding protein of rat ventral **prostate**
AUTHOR(S): Heyns, Walter; Bossyns, Denise; Peeters, Ben; Rombauts, Wilfried
CORPORATE SOURCE: Fac. Geneeskunde, Kathol. Univ. Leuven, Louvain, B-3000, Belg.
SOURCE: Journal of Biological Chemistry (1982), 257(13), 7407-13
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A proline-rich polypeptide associated with prostatic binding protein in the rat ventral **prostate** was purified. Its mol. weight estimated by gel filtration is .apprx.8500, but a markedly **lower** value (3300) is obtained by SDS-urea polyacrylamide gel electrophoresis. Isoelec. focusing on thin-layer polyacrylamide gels yields 2 major forms with isoelec. points of, resp., 7.75 and 7.05. The amino acid composition of proline-rich polypeptide is characterized by a high (19.5%) proline content, and its N2-terminal amino acid is glycine. Like prostatic binding protein, proline-rich polypeptide is a characteristic component of the rat ventral **prostate** and is localized primarily in the intraluminal secretion of this gland. In intact adult male rats, the cytosol of a whole gland contains 0.70 mg of the polypeptide, as measured by radial immunodiffusion, or 2.6 of the total protein. This amount decreases gradually after castration and becomes undetectable after 8 days. Androgen treatment, on the other hand, results in a rapid stimulation, whereas **estradiol** and progesterone are ineffective. Proline-rich polypeptide is markedly more **androgen-dependent** than prostatic binding protein.

L39 ANSWER 25 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1980:191776 HCAPLUS
DOCUMENT NUMBER: 92:191776
TITLE: Differential effects of estrogen treatment on canine seminal plasma components
AUTHOR(S): Isaacs, John T.; Isaacs, William B.; Wheaton, Lynn G.; Coffey, Donald S.
CORPORATE SOURCE: James Buchanan Brady Urol. Inst., Johns Hopkins Univ., Baltimore, MD, USA
SOURCE: Investigative Urology (1980), 17(6), 495-8
CODEN: INURAQ; ISSN: 0021-0005
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB In castrate dogs, complete **androgen-dependent** restoration of seminal plasma content of fluid, electrolytes, and protein was induced by testosterone [58-22-0] treatment alone. In contrast, a combination of androgen and estrogen treatment selectively **reduced** only the androgen-induced stimulation of the electrolyte and fluid components without altering the total amount of protein secreted. Spontaneous cystic prostatic hyperplasia was characterized by a similar decrease in total fluid and electrolyte content without a concomitant decrease in the total amount of protein in the seminal plasma. Prostatic protein secretion may be a process distinct from electrolyte-fluid transport because either **estradiol** (I) [**50-28-2**] treatment or the development of spontaneous cystic prostatic hyperplasia dissocs. these 2 processes.

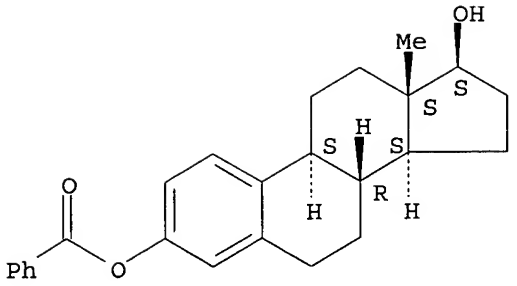
L39 ANSWER 26 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1976:537717 HCAPLUS
DOCUMENT NUMBER: 85:137717
TITLE: **Androgen-dependent** accumulation of carnitine by rat epididymis after injection of [3H]-butyrobetaine in vivo
AUTHOR(S): Boehmer, Thomas; Hansson, Vidar
CORPORATE SOURCE: Rikshosp., Univ. Oslo, Oslo, Norway
SOURCE: Molecular and Cellular Endocrinology (1975), 3(2), 103-15
CODEN: MCEND6; ISSN: 0303-7207
DOCUMENT TYPE: Journal
LANGUAGE: English

AB After i.m. injection of butyrobetaine [407-64-7] into rats, the accumulation of carnitine (I) [461-06-3] into the epididymis, **prostate** gland, seminal vesicles, testis, and heart was studied. The concentration of radiolabeled I into the cauda epididymis increased linearly with time up to 72 hr after the injection of the precursor, whereas its level in the **prostate** and seminal vesicles decreased rapidly. Very low levels of I were found in the testis. Castration **reduced** the I accumulation by cauda epididymis to 6% of the control levels, whereas treatment of castrated animals with testosterone propionate [57-85-2] (500 μg/day) partly restored the I uptake. Similar treatment with 17β- **estradiol** valerate [**979-32-8**] or 17α-hydroxyprogesterone [68-96-2] had no effect. Surprisingly, cyproterone acetate [427-51-0] (5 mg/day) also significantly stimulated I accumulation by the epididymis to a level above that of the castrated controls. Simultaneous injection of both cyproterone acetate and testosterone propionate to castrated animals caused an additive effect of these steroids. This indicated that cyproterone acetate in this system is working as a weak androgen. Treatment of rats with 17β- **estradiol** valerate also decreased I accumulation by the cauda epididymis. This is due to suppression of pituitary gonadotropin

secretion, since concomitant treatment with testosterone propionate (500 μg/day) caused a normalization of the I uptake. Treatment of intact rats with cyproterone acetate significantly decreased the epididymal weight, but not the I accumulation. 17α-Hydroxyprogesterone treatment had no effect either on the epididymal weight or the accumulation of I. Unilateral orchiectomy decreased the I accumulation by the cauda epididymis to .apprx.40% of that occurring in the nonoperated control side. This indicates that the luminal contact between the testis and epididymis or the luminal content of the epididymis itself is of importance for the **androgen-dependent** metabolic process occurring in the cauda epididymis. Castration or hormone treatment did not change the conversion of butyrobetaine to I or the I uptake by heart. I uptake by the testis after butyrobetaine injection was rather low and this would exclude the possibility of synthesis of I in the testis as a source of epididymal I. I only accumulated in the cauda epididymis in vivo 4 to 96 hr after injection of butyrobetaine. The presence of radioactively labeled butyrobetaine or methylcholine was not detected.

L39 ANSWER 27 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1975:54907 HCAPLUS
DOCUMENT NUMBER: 82:54907
TITLE: Different mechanisms of regulation of nuclear reduced nicotinamide-adenine dinucleotide phosphate-dependent 3-oxosteroid 5α-reductase activity in rat liver, kidney, and **prostate**
AUTHOR(S): Gustafsson, Jan A.; Pousette, Ake
CORPORATE SOURCE: Dep. Chem., Karolinska Inst., Stockholm, Swed.
SOURCE: Biochemical Journal (1974), 142(2), 273-7
CODEN: BIJOAK; ISSN: 0264-6021
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of age, sex, castration, and treatment with androgens and estrogens on the nuclear metabolism of androstenedione in kidney, liver, and **prostate** suggested that nuclear 5α-reductase (I) is under the control of distinctly different regulatory mechanisms in the 3 tissues. Hepatic I, which was greater in females than in male rats and increased with age in females, was increased by castration but unaffected by testosterone propionate (II) (400 μg/day for 7 days); renal I was unaffected by age, sex, castration, or II, and prostatic I was **androgen-dependent**, decreasing after castration and increasing after II-treatment. The functions of I in the 3 tissues are discussed.
IT **50-50-0**
RL: BIOL (Biological study)
(ketosteroid **reductase** response to, in organs, regulation of)
RN 50-50-0 HCAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol (17β)-, 3-benzoate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L39 ANSWER 28 OF 28 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1967:328 HCAPLUS
DOCUMENT NUMBER: 66:328
TITLE: Influence of estrogens on **androgen-dependent** fructose formation in sex accessory organs
AUTHOR(S): Thomas, John Arlen; Knych, Edward T., Jr.
CORPORATE SOURCE: Sch. of Med., Creighton Univ., Omaha, NE, USA
SOURCE: Acta Endocrinologica (1966), 53(3), 455-61
CODEN: ACENA7; ISSN: 0001-5598
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Subcutaneous injection of testosterone (I) stimulated the formation of fructose (II) in castrate mice, but the combined treatment of I and estrogen significantly **reduced** the levels of II in the anterior **prostate.** Estrogens were more effective in counteracting the action of I when injected earlier rather than late after castration. Ethynylestradiol and **estradiol** benzoate were more effective in counteracting I than estriol, estrone, diethylstilbestrol. A greater **reduction** in II levels were observed when **lower** doses of injected I were simultaneously administered with estrogen. In the seminal vesicles a synergistic action between I and various estrogens on II levels was observed, although antagonism was also evident. Increasing the period of time between castration and initial injection enhanced the synergistic action of the 2 hormones. Thus, there are differences in sex accessory organs response with regard to the II levels following the simultaneous injections of I and various estrogens.

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=> d his ful

     (FILE 'REGISTRY' ENTERED AT 17:35:37 ON 26 JUL 2005)
                DEL HIS Y
L1              STR
L2           19 SEA SSS SAM L1
L3              STR L1
L4           12 SEA SSS SAM L3
L5          408 SEA SSS FUL L1
                SAV TEMP L5 COOK152FUL/A
L6              STR L3
L7          225 SEA SUB=L5 SSS FUL L6

     FILE 'HCAPLUS' ENTERED AT 18:07:53 ON 26 JUL 2005
L8         1454 SEA ABB=ON  PLU=ON  L7
                E PROSTATE CANCER/CV
                E E3+ALL/CV
L9        42118 SEA ABB=ON  PLU=ON  ("PROSTATE CANCER"/CV OR "PROSTATE GLAND,
                NEOPLASM"/CV) OR PROSTATE?
L10          16 SEA ABB=ON  PLU=ON  L8(L)L9

     FILE 'HCAPLUS' ENTERED AT 18:11:56 ON 26 JUL 2005
                D STAT QUE
                D IBIB ABS HITSTR L10 1-16

     FILE 'STNGUIDE' ENTERED AT 18:27:59 ON 26 JUL 2005

     FILE 'REGISTRY' ENTERED AT 18:38:49 ON 26 JUL 2005
L*** DEL       0 S L8(L)PRODRUG

     FILE 'HCAPLUS' ENTERED AT 18:39:16 ON 26 JUL 2005
L11            4 SEA ABB=ON  PLU=ON  L8(L)PRODRUG
L12            3 SEA ABB=ON  PLU=ON  L11 NOT L10
                D STAT QUE
                D IBIB ABS HITSTR L12 1-3
L13           30 SEA ABB=ON  PLU=ON  (L8 AND PRODRUG) NOT (L10 OR L12)

     FILE 'REGISTRY' ENTERED AT 18:41:15 ON 26 JUL 2005
                E ESTRADIOL
L14         1277 SEA ABB=ON  PLU=ON  ESTRADIOL/BI

     FILE 'HCAPLUS' ENTERED AT 18:41:43 ON 26 JUL 2005
L15        84636 SEA ABB=ON  PLU=ON  L14 OR ESTRADIOL
L16        18241 SEA ABB=ON  PLU=ON  L15(L)(LOWER? OR REDUC?)
L17         1747 SEA ABB=ON  PLU=ON  L15(2A)(LOWER? OR REDUC?)
L18          301 SEA ABB=ON  PLU=ON  L15 (2W)LOWER?
                D KWIC
L19            0 SEA ABB=ON  PLU=ON  L15(2W)LOWERING(2W)(?DRUG? OR ?PHARMA? OR
                ?MEDICIN?)
L20           20 SEA ABB=ON  PLU=ON  L15(2W)LOWERING
L21            2 SEA ABB=ON  PLU=ON  (L15(2A)LOWERING)(L)(?DRUG? OR ?PHARMA? OR
                ?MEDICIN?)
                D SCAN
                D KWIC
                E ESTRADIOL LOW/CV
                E ESTRADIOL/CV
                E E3+ALL/CV
                E ANTIESTRADIOL
                E ANTIESTRADIOL/CV
L22          579 SEA ABB=ON  PLU=ON  L16 AND L9

     FILE 'REGISTRY' ENTERED AT 18:49:19 ON 26 JUL 2005
                E GHRH
L23          108 SEA ABB=ON  PLU=ON  GHRH/BI
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     FILE 'HCAPLUS' ENTERED AT 18:49:29 ON 26 JUL 2005
L24         2096 SEA ABB=ON  PLU=ON  L23 OR GHRH
L25            0 SEA ABB=ON  PLU=ON  L24 AND L22
L26            0 SEA ABB=ON  PLU=ON  L24 AND L15 AND L9
L27           96 SEA ABB=ON  PLU=ON  L24 AND L15
                 E ANDROGEN DEPENDENT/CV
                 E PROSTATE CANCER/CV
                 E PROSTATE A/CV
L28           10 SEA ABB=ON  PLU=ON  "PROSTATE ANDROGEN-REGULATED PROTEIN"+ALL/C
                 V
                 E E3+ALL/CV
                 E E6+ALL/CV
L29           10 SEA ABB=ON  PLU=ON  ("PROSTATE ANDROGEN-REGULATED PROTEIN"/CV
                 OR "PROTEINS (L) JTB (JUMPING TRANSLOCATION BREAKPOINT)"/CV)
L30         1900 SEA ABB=ON  PLU=ON  ANDROGEN(L)DEPENDENT(L)L9
L31         5840 SEA ABB=ON  PLU=ON  L9(L)(?DRUG? OR ?PHARMA? OR ?MEDICIN? OR
                 CHEMOPREVENT?)
L32          320 SEA ABB=ON  PLU=ON  L30 AND L31
L33         2151 SEA ABB=ON  PLU=ON  ANDROGEN(W)DEPENDENT
L34          165 SEA ABB=ON  PLU=ON  L33 AND L32
L35          168 SEA ABB=ON  PLU=ON  L33 AND L31
L36           71 SEA ABB=ON  PLU=ON  L35 AND ANDROGEN(W)INDEPENDENT
                 D KWIC
L37            5 SEA ABB=ON  PLU=ON  L36 AND PRODRUG
                 D KWIC
                 D STAT QUE
                 D IBIB ABS HITSTR L37 1-5
                 D SCAN
L38           28 SEA ABB=ON  PLU=ON  L22 AND L33
L39           28 SEA ABB=ON  PLU=ON  L38 NOT L37
                 D KWIC
                 D KWIC 2
                 D KWIC 3
                 D KWIC 4
                 D STAT QUE
                 D IBIB ABS HITSTR L39 1-28

     FILE HCAPLUS

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     LAST RELOADED: Jul 22, 2005 (20050722/UP).

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
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* available and contains the CA role and document type information. *
*
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Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
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